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Health and Environmental
Effects Profile for Benzyl Chloride

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16. ABSTRACT The Health and Environmental Effects Profile for <u>Benzyl Chloride</u> was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents. Quantitative estimates have been presented provided sufficient data are available. <u>Benzyl chloride</u> has been evaluated as a carcinogen. The human carcinogen potency factor (q1*) for <u>benzyl chloride</u> is 1.71×10^{-2} (mg/kg/day)⁻¹ for oral exposure. The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for <u>benzyl chloride</u> is 1000.			
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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE
FOR BENZYL CHLORIDE

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEP's are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents. The literature searched and the dates of the searches are included in the section titled "Appendix: Literature Searched."

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEP's will become part of the EPA RCRA docket.

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EXECUTIVE SUMMARY

Benzyl chloride, a colorless liquid with irritating vapors (Gelfand, 1979), is manufactured commercially in the United States. The demand for the compound in the United States was 72 million pounds in 1984 (CMR, 1984). The three U.S. manufacturers of benzyl chloride (Monsanto, Stauffer Chemical and Velsicol Chemical) have a combined annual capacity of 152 million pounds (CMR, 1984). Benzyl chloride is used as a chemical intermediate in the production of benzyl compounds with the synthesis of butyl benzyl phthalate being the most important application (CMR, 1984).

Benzyl chloride is not expected to persist in the environment because of its reactivity. In water, the dominant removal mechanism is hydrolysis; benzyl chloride has an experimental hydrolytic half-life ranging from 19.1 to 1.1 days at respective temperature ranges of 0.1-20°C (Robertson and Scott, 1961; Albery and Curran, 1972). Benzyl chloride is readily biodegraded by active sludge and sewage (Sasaki, 1978; Kitano, 1978; Jacobson and Alexander, 1981). Volatilization of benzyl chloride from water is expected to occur, but at a slower rate than hydrolysis. Bioaccumulation in aquatic organisms and adsorption to sediment and suspended matter is not expected to be significant.

The dominant removal mechanism of benzyl chloride in the atmosphere is its reaction with OH• radicals (Singh et al., 1982). With respect to OH• radical reaction, the atmospheric residence time of benzyl chloride is 3.0-3.9 days (Atkinson et al., 1982; Cupitt, 1980); it is estimated to be >289 days with respect to ozone reaction (Atkinson et al., 1982).

Data based on its fate in water and its physical properties suggest that benzyl chloride is susceptible to both hydrolytic decomposition and significant leaching in moist soils in the absence of degradative mechanisms.

Benzyl chloride has been detected in industrial wastewater effluents (IARC, 1982), in Delaware river water (Sheldon and Hites, 1978), in sediment/soil/water from the Love Canal (Hauser and Bromberg, 1983) and in surface water in a few areas in New Jersey (Pellizzari et al., 1979). The presence of benzyl chloride is attributed to industrial release and dumping. The lack of monitoring data on benzyl chloride in water is consistent with the rapid degradation of benzyl chloride by hydrolysis.

Benzyl chloride is emitted to the atmosphere from industrial production and use sources at a rate of 45,000 pounds/year (Anderson, 1983). While low levels of benzyl chloride have been detected in urban air samples, the fact that it is not generally detected is consistent with its rapid degradation by OH• radicals in the atmosphere (Singh et al., 1982).

The information available concerning toxicity of benzyl chloride to aquatic organisms is limited. LC₅₀ values for three fish species are 3-16 mg/L. The lowest nominal concentration at which adverse effects were reported was 1.3 mg/L, the EC₅₀ for immobilization of Daphnia magna (Bringmann and Kuehn, 1982).

Benzyl chloride was extensively absorbed from the gastrointestinal tract of rats and rabbits following oral dosing; ~70 and 86%, respectively, of the administered dose was recovered as metabolites in the urine collected over 24 hours (Bunner and Creasia, 1982; Bray et al., 1958). Following absorption, benzyl chloride was widely distributed to organs and tissues of rats (Bunner and Creasia, 1982). Although excretion of metabolites by rats (Bunner and Creasia, 1982) and rabbits (Bray et al., 1958) was essentially complete at 24 hours after dosing, radioactivity was still detectable in all organs and tissues of rats dosed with [¹⁴C]-benzyl chloride (Bunner and Creasia, 1982). The main urinary metabolite of rats and rabbits was a

mercapturic acid conjugate (Barnes et al., 1959; Bray et al., 1958), formed by conjugation of benzyl chloride with glutathione in the liver (Boyland and Chasseaud, 1969). Other urinary metabolites in rabbits were glycine conjugates and glucosiduronic acid conjugates (Bray et al., 1958). Increased amounts of hippuric acid were detected in the urine of rats after oral dosing with benzyl chloride (Maitrya and Vyas, 1970). At 24 hours after oral dosing with [^{14}C]-benzyl chloride, ~70% of the dose of radioactivity was detected in the urine and ~15% was detected in the feces of rats (Bunner and Creasia, 1982).

A 2-year NCI bioassay (Lijinsky, 1985) provided convincing evidence of the carcinogenic potential of benzyl chloride in mice treated by gavage with 50 or 100 mg/kg/day, 3 days/week. Dose-related increases in the incidences of forestomach carcinomas and carcinomas/papillomas in both sexes were observed. Treated male mice had increased incidences of liver and circulatory system tumors, whereas high-dose females showed a marginally increased occurrence of pulmonary adenomas/carcinomas. Female rats treated with 15 or 30 mg/kg/day, 3 days/week, had a dose-related increased incidence of C-cell adenoma/carcinoma of the thyroid. Human studies (Sakabe et al., 1976; Sakabe and Fukuda, 1977; Sorahan et al., 1983; Wong and Morgan, 1984) have shown that occupational exposure to halogenated intermediates in benzoyl chloride production may increase the risk of respiratory cancer-induced mortality.

Benzyl chloride was weakly mutagenic to bacterial strains Salmonella typhimurium TA100 and Escherichia coli WP2 $\mu\text{vr A(p)}$, which are sensitive to the induction of point mutations (Venitt, 1982). It also expressed genotoxicity toward repair-deficient strains (Fluck et al., 1976; Rosenkranz and Leifer, 1980). Parry and Wilcox (1982) reported that benzyl chloride

affects the replicative and repair mechanisms in fungi. In Drosophila melanogaster, benzyl chloride was found to induce somatic mutations more readily than sex-linked alterations (Fahmy and Fahmy, 1982). In mammalian culture, benzyl chloride was slightly mutagenic to DNA excision-repair deficient strains of CHO cells (Hoy et al., 1984), but was generally ineffective in altering unscheduled DNA synthesis (Mitchell, 1976; Booth et al., 1983). Scott and Topham (1982) concluded that benzyl chloride was generally not mutagenic in in vivo mammalian systems, including the mouse micronucleus and sperm head abnormality tests.

Leonskaya (1980) found that an oral dose of 208 mg/kg/day on days 1-19 of gestation in rats led to increases in embryonic mortality and developmental defects in surviving fetuses. Doses of 0.0006 and 0.006 mg/kg/day were reported to increase embryonic mortality and induce a slightly increased incidence of wavy ribs, although no supporting data for the former statement were provided. A dose of 0.00006 mg/kg/day was without effect.

Gavage administration of benzyl chloride in rats at 0.6 mg/kg/day for 6 months led to changes in serum enzymes and whole blood inorganic phosphate levels (Rudnev et al., 1979). Oral doses of 250 and 125 mg/kg benzyl chloride, 3 times/week, were rapidly fatal to rats (Bunner and Creasia, 1982; Lijinsky, 1985). At ≥ 15 mg/kg, rats had hyperplasia and/or hyperkeratosis of the forestomach and hyperplasia and/or focal necrosis of the heart. Lijinsky (1985) also treated male and female mice with benzyl chloride by gavage 3 times/week for 6-8 months. Doses of 125 and 250 mg/kg were fatal to all rats, whereas the mice exposed to the lowest dose (100 mg/kg) survived. In mice, the only treatment-related pathological effect was hepatic hyperplasia. In a subsequent 2-year bioassay, Lijinsky (1985) observed no non-neoplastic effects at oral doses of up to 30 mg/kg/day

benzyl chloride for 3 days/week in rats. Mice not otherwise afflicted with forestomach tumors showed forestomach hyperplasia at 50 or 100 mg/kg/day, 3 days/week.

Oral LD_{50} values in rats, mice and rabbits after acute benzyl chloride administration range from 625-1624 mg/kg (Rudnev et al., 1979; Back et al., 1972). A 2-hour inhalation exposure to 100 mg/m³ caused weight gain inhibition in 10 white rats (Mikhailova, 1965); higher doses caused mucosal irritation, delayed respiration and nervous system manifestations. An occupational study suggested that short exposures to as little as 6-8 mg/m³ are dangerous to mucous membranes (Mikhailova, 1971). At least two studies (Laudsteiner and Jacobs, 1936; Rudnev et al., 1979) have demonstrated the sensitization potential of benzyl chloride in rodents. Fiala et al. (1982) observed feedback inhibition of glutathione as a result of increased γ -glutamyl transferase activity after benzyl chloride administration. The degree of DNA alkylation in mouse testes and brain was significantly elevated over hemoglobin levels 1 hour after intravenous injection of benzyl chloride (Wallis, 1981).

An RQ for chronic toxicity of 1000 was derived based on the observation of myocardial necrosis in rats treated with ≥ 15 mg/kg/day, 3 days/week for 6 months (Lijinsky, 1985; Bunner and Creasia, 1982). A q_1^* of 1.71×10^{-1} (mg/kg/day)⁻¹ was derived from the dose-response data for C-cell tumors of the thyroid of female rats in the study by Lijinsky (1985). An F factor of 8.68×10^{-1} (mg/kg/day)⁻¹ was derived from the dose-response data for squamous cell tumors of the stomach in male mice in the Lijinsky (1985) study. Benzyl chloride is an IARC group 2B chemical with a LOW hazard ranking under CERCLA. According to the U.S. EPA, CAG scoring system this compound would be ranked as B2, probable human carcinogen.

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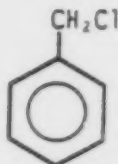
LIST OF ABBREVIATIONS

BCF	Bioconcentration factor
CAS	Chemical Abstract Service
CHO	Chinese hamster ovary
CS	Composite score
DNA	Deoxyribonucleic acid
EC ₅₀	Concentration effective to 50% of recipients (and all other subscripted concentration levels)
K _{oc}	Soil sorption coefficient
K _{ow}	Octanol/water partition coefficient
LC ₅₀	Concentration lethal to 50% of recipients (and all other subscripted dose levels)
LD ₅₀	Dose lethal to 50% of recipients
MED	Minimum effective dose
ppb	Parts per billion
ppm	Parts per million
ppt	Parts per trillion
RQ	Reportable quantity
RV _d	Dose-rating value
RV _e	Effect-rating value
SMR	Standard mortality ratio
TLV	Threshold limit value
TWA	Time-weighted average
UV	Ultraviolet
WS	Water solubility

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Benzyl chloride is the common chemical name, but this compound is also known as α -chlorotoluene, chloromethyl benzene, chlorophenylmethane and α -tolyl chloride (HSDB, 1985). The structure, molecular weight, empirical formula and CAS Registry number for benzyl chloride are as follows:



Molecular weight: 126.59

Empirical formula: $\text{C}_7\text{H}_7\text{Cl}$

CAS Registry number: 100-44-7

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Benzyl chloride is a colorless liquid with a very pungent odor. Its vapors are irritating to the eyes and mucous membranes, classifying benzyl chloride as a powerful lachrymator (Gelfand, 1979). The air odor threshold value is 0.047 ppm with 50% of test subjects detecting an odor at a concentration of 0.01 ppm and 100% at 0.047 ppm (Verschuere, 1983). At room temperature, benzyl chloride is miscible with most organic solvents (Gelfand, 1979). Selected physical properties are listed below:

Freezing point:	-39.2°C	Gelfand, 1979
Boiling point:	179.4°C	Gelfand, 1979
Density (20/20°C):	1.1002 g/cm ³	IARC, 1982
Refractive index (20°C):	1.5392	Gelfand, 1979
Vapor pressure:		
at 22°C	1.0 mm Hg	Perry and Green, 1984
at 25°C	1.3 mm Hg	MacKay et al., 1982
Flash point:	67°C (closed cup)	Gelfand, 1979
	74°C (open cup)	Gelfand, 1979

Lower Flammability limit:	1.1% by volume in air	Gelfand, 1979
Water solubility:		
at 4.5°C	331 ppm	Ohnishi and Tanabe, 1971
at 20°C	493 ppm	Ohnishi and Tanabe, 1971
at 30°C	555 ppm	Ohnishi and Tanabe, 1971
Log K _{ow} :	2.30	Hansch and Leo, 1981
Air conversion factor:	1 ppm = 5.17 mg/m ³	

Benzyl chloride undergoes reactions both at the side chain containing the chlorine and the aromatic ring (Gelfand, 1979). It reacts with many metals and rapidly decomposes when heated in the presence of iron (OHMTADS, 1986). Benzyl chloride decomposes in hot water, yielding benzyl alcohol (IARC, 1982).

1.3. PRODUCTION DATA

Benzyl chloride has been produced commercially in the United States since ~1919 (IARC, 1982). The most recent production figure available is 80.4 million pounds in 1972 (USTC, 1974). Demand for benzyl chloride in the United States was 72 million pounds in 1984 and is expected to increase growth to ~82 million pounds by 1988 (CMR, 1984). Imports of benzyl chloride through principal U.S. custom districts in 1983 totalled 1.5 million pounds (USITC, 1984). The current United States manufacturers of benzyl chloride and their respective annual capacities are as follows (CMR, 1984; SRI, 1985):

	Capacity (million lbs)
Monsanto Co. (Bridgeport, NJ)	100
Stauffer Chem. Co. (Edison, NJ)	22
Velsicol Chem. Corp. (Chattanooga, TN)	30
Total:	152

Benzyl chloride is manufactured by the thermal or photochemical chlorination of toluene. The crude product resulting from the toluene chlorination is purged of dissolved HCl, neutralized with alkali, and distilled for purification. Lime, sodium carbonate and triethylamine are used as stabilizers during storage and shipment (Gelfand, 1979).

1.4. USE DATA

The use pattern for benzyl chloride in the United States is presented in Table 1-1. Benzyl chloride is used as an intermediate in the manufacture of certain dyes and is also used as an intermediate for the manufacture of pharmaceutical, perfumes and flavor products (Gelfand, 1979).

1.5. SUMMARY

Benzyl chloride, a colorless liquid with irritating vapors (Gelfand, 1979), is manufactured commercially in the United States. The demand for the compound in the United States was 72 million pounds in 1984 (CMR, 1984). The three U.S. manufacturers of benzyl chloride (Monsanto Co., Stauffer Chemical Co. and Velsicol Chemical Corp.) have a combined annual capacity of 152 million pounds (CMR, 1984). Benzyl chloride is used as a chemical intermediate in the production of benzyl compounds with the synthesis of butyl benzyl phthalate being the most important application (CMR, 1984).

TABLE 1-1
Use Pattern for Benzyl Chloride in the United States*

Use	Percent
Butyl benzyl phthalate	60
Benzyl alcohol	12.5
Quarternary ammonium compounds	11
Benzyl cyanide	3
Other (including benzyl acetate, benzyl salicylate and benzyl cinnamate)	13.5

*Source: CMR, 1984

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. WATER

2.1.1. Hydrolysis. Based on the results of hydrolysis studies, hydrolysis is expected to be a major process in the removal of benzyl chloride from water. Table 2-1 lists the experimentally determined neutral hydrolysis rate constants reported by several authors along with the respective estimated half-lives. The rate of hydrolysis accelerates with an elevation of temperature; the half-life at 0.1°C is 19.10 days while the half-life at 20°C is 1.14 days. Tanabe and Sano (1962) investigated the hydrolysis of benzyl chloride in pure water over the pH range from 0-14; the rate of hydrolysis was found to be independent of pH up to pH 13.0. In aqueous solution, the products of hydrolysis are benzyl alcohol and hydrogen chloride (Tanabe and Sano, 1962; Alberly and Curran, 1972).

2.1.2. Oxidation. Pertinent data regarding the oxidation of benzyl chloride in water could not be located in the available literature as cited in the Appendix.

2.1.3. Photolysis. Data pertaining to the aquatic photolysis of benzyl chloride could not be located in the available literature. Cupitt (1980) suggested the possibility of atmospheric photolysis of benzyl chloride. Appleton et al. (1980) reported that acetone-photosensitized photolysis of benzyl chloride occurs at 300 nm in an alcohol solution. These data suggest that benzyl chloride may be susceptible to sensitized photoreaction in water, even if direct photolysis proves unimportant. More experimental data are required to determine the sensitized photolysis rate and its comparative significance. (It is unlikely, however, that photolysis will occur as rapidly as hydrolysis.)

TABLE 2-1
Neutral Hydrolysis of Benzyl Chloride

Temperature (°C)	Hydrolysis Rate Constant (sec ⁻¹)	Estimated Half-Life (days)	Reference
15	0.356x10 ⁻⁵	2.25	Robertson and Scott, 1961
20	0.703x10 ⁻⁵	1.14	
25	1.38 x10 ⁻⁵	0.58	
25	1.246x10 ⁻⁵	0.64	Koskikallio, 1967
40	7.27 x10 ⁻⁵	0.11	
4	0.077x10 ⁻⁵	10.42	Albery and Curran, 1972
0.1	0.042x10 ⁻⁵	19.10	

2.1.4. **Microbial Degradation.** From the tests performed under the Japanese MITI protocol, Sasaki (1978) reported that benzyl chloride was "well-biodegradable," indicating that oxygen consumption 2 weeks after test initiation was >30%. In the MITI test, 100 ppm of the test substance was incubated at 25°C with 30 ppm of an active sludge seed for 2 weeks. Kitano (1978) used the same test conditions and concluded that benzyl chloride was biodegradable. Jacobson and Alexander (1981) used raw sewage and raw sewage acclimated to various nonchlorinated compounds to determine that benzyl chloride biodegraded significantly with the formation of dechlorinated products during a 2-day incubation period. For example, sewage microflora acclimated to benzoic acid released 44% of the organic chlorine as inorganic chloride after 2 days.

The above biodegradation studies indicate that benzyl chloride is biodegradable by active sludge and sewage; however, these studies do not predict the relative importance of benzyl chloride biodegradation in natural waters.

2.1.5. **Volatilization.** Calculating Henry's Law constant from the vapor pressure (1.0 mm Hg at 22°C) and water solubility (493 ppm at 20°C) of benzyl chloride yields a value of 3.4×10^{-4} atm·m³/mol, suggesting that volatilization from water may be significant, although the rate of evaporation may not be rapid (Lyman et al., 1982).

2.1.6. **Adsorption.** Benzyl chloride is predicted to have a medium to high mobility in soil (Section 2.3.2.). Therefore, partitioning of benzyl chloride from the water column to suspended organic matter or to sediment is not expected to be significant.

2.1.7. **Bioconcentration.** Experimental data regarding the bioconcentration of benzyl chloride in aquatic organisms could not be located in the available literature. The following two regression equations, however, can be used for estimating the BCF of an organic compound (Lyman et al., 1982):

$$\text{Log BCF} = 0.76 \text{ Log } K_{ow} - 0.23 \quad (2-1)$$

$$\text{Log BCF} = 2.791 - 0.564 \text{ Log WS (in ppm)} \quad (2-2)$$

Using 2.30 as $\text{Log } K_{ow}$ and 493 ppm as the WS, the BCF values calculated from Equations (2-1) and (2-2) are 33 and 16, respectively, suggesting that bioaccumulation of benzyl chloride in aquatic organisms will not be significant.

2.2. AIR

2.2.1. **Chemical Removal Processes.** The dominant removal mechanism for benzyl chloride in the atmosphere is its reaction with $\text{OH}\cdot$ radicals (Singh et al., 1982). Atkinson et al. (1982) estimated the atmospheric residence time of benzyl chloride in a typical atmosphere containing 10^6 $\text{OH}\cdot$ radicals/ cm^3 to be ~3 days, assuming the rate constant for this reaction was similar to the rate constant for $\text{OH}\cdot$ radical addition to toluene. Cupitt (1980) theoretically calculated the rate constant for the OH -benzyl chloride reaction to be $\sim 3 \times 10^{-12}$ $\text{cm}^3/\text{molecule-sec}$, which corresponds to an atmospheric residence time of 3.9 days (half-life of ~2.7 days) in a typical atmosphere (10^6 $\text{OH}\cdot$ radicals/ cm^3).

Atkinson et al. (1982) experimentally determined the rate constant for the reaction between benzyl chloride and ozone to be $< 0.04 \times 10^{-18}$ $\text{cm}^3/\text{molecule-sec}$. In a typical atmosphere containing 10^{12} ozone molecules/ cm^3 , the atmospheric residence time is calculated to be >289 days and the half-life is calculated to be >200 days. Thus, reaction with ozone is not a competitive removal mechanism in comparison with $\text{OH}\cdot$ reaction.

Pertinent data regarding the rate of photolysis of benzyl chloride in the atmosphere could not be located in the available literature as cited in the Appendix; however, Cupitt (1980) reported that the photolysis of benzyl chloride in the atmosphere is possible.

2.2.2. **Physical Removal Processes.** Cupitt (1980) suggested that the physical removal processes for benzyl chloride in the atmosphere are unlikely to be significant when compared with removal through OH• radical reaction.

2.3. SOIL

Pertinent data regarding the fate and transport of benzyl chloride in soil could not be located in the available literature as cited in the Appendix. Therefore, prediction of its fate in soil are based on its physical properties or its predicted fate in water.

2.3.1. **Chemical and Microbial Degradation.** In water, benzyl chloride undergoes significant hydrolysis independent of pH (see Section 2.1.1.). Therefore, it is likely to experience hydrolytic decomposition in moist soil, with the rate of hydrolysis dependent primarily on the temperature of the soil.

Benzyl chloride is biodegradable by active sludge or sewage in water (see Section 2.1.4.), but direct analogy to biodegradation in the soil is not possible. Microbial decomposition by soil microbiota does, however, seem possible, but experimental data are required to ascertain its importance.

2.3.2. **Adsorption.** Table 2-2 lists four regression equations used in estimating K_{oc} values for benzyl chloride. The estimated K_{oc} values are reasonably close ranging from 123-482. In addition, estimating a K_{oc} from the molecular topology and quantitative structure-activity analysis method

TABLE 2-2
Estimations of K_{OC} for Benzyl Chloride^{a,b}

Regression Equation	Estimated K_{OC} Value
$\text{Log } K_{OC} = 3.64 - 0.55 \text{ Log WS (in ppm)}$	144
$\text{Log } K_{OC} = 3.44 - 0.54 \text{ Log WS (in mol fraction)}$	482
$\text{Log } K_{OC} = 0.544 \text{ Log } K_{OW} + 1.377$	425
$\text{Log } K_{OC} = 1.00 \text{ Log } K_{OW} - 0.21$	123

^aSource: Lyman et al., 1982

^b $\text{Log } K_{OW} = 2.30$ and $\text{WS} = 493 \text{ ppm}$

of Sabljic (1984) yields a value of 410. These K_{oc} values predict that benzyl chloride will have a medium to high mobility in soil (Swann et al., 1983) and will therefore be susceptible to significant leaching in the absence of degradative mechanisms.

2.3.3. Photolysis and Volatilization. Surface photolysis of benzyl chloride is possible; however, photolysis is not likely to be important because of soil hydrolysis.

Since benzyl chloride is relatively volatile at ambient temperatures, evaporation from dry soil surfaces is expected because benzyl chloride is not expected to be tightly adsorbed to soil. Volatilization from moist soils may also occur, but will be insignificant compared with its hydrolysis.

2.4. SUMMARY

Benzyl chloride is not expected to persist in the environment because of its reactivity. In water, the dominant removal mechanism is hydrolysis; benzyl chloride has an experimental hydrolytic half-life ranging from 19.1 to 1.1 days at respective temperature ranges of 0.1-20°C (Robertson and Scott, 1961; Albery and Curran, 1972). Benzyl chloride is readily biodegraded by active sludge and sewage (Sasaki, 1978; Kitano, 1978; Jacobson and Alexander, 1981). Volatilization of benzyl chloride from water is expected to occur, but at a slower rate than hydrolysis. Bioaccumulation in aquatic organisms and adsorption to sediment and suspended matter is not expected to be significant.

The dominant removal mechanism of benzyl chloride in the atmosphere is its reaction with OH• radicals (Singh et al., 1982). With respect to OH• radical reactions, the atmospheric residence time of benzyl chloride is 3.0-3.9 days (Atkinson et al., 1982; Cupitt, 1980) and it is estimated to be >289 days with respect to ozone reaction (Atkinson et al., 1982).

Data based on its physical properties and fate in water suggest that it is susceptible to both hydrolytic decomposition and significant leaching in moist soils in the absence of degradative mechanisms.

3. EXPOSURE

Benzyl chloride has not been detected in nature (IARC, 1982). Occupationally, ~3000 workers in the United States are potentially exposed to benzyl chloride resulting from its manufacture and use (IARC, 1982).

3.1. WATER

Benzyl chloride has been identified in industrial and oil refinery effluents (IARC, 1982). Benzyl chloride has also been detected in a water sample (concentration not reported) collected from the Delaware River in October, 1976 (Sheldon and Hites, 1978), in sediment/soil/water samples from the Love Canal (Hauser and Bromberg, 1983) and in water from several New Jersey locations (Pellizzari et al., 1979). The presence of benzyl chloride in these samples is attributed to industrial release or dumping of the compound.

The U.S. EPA STORET Data Base lists no observations for benzyl chloride. The lack of monitoring data in water is consistent with the fact that benzyl chloride degrades rapidly through hydrolysis.

3.2. FOOD

Pertinent data regarding the monitoring of benzyl chloride in food could not be located in the available literature as cited in the Appendix.

3.3. INHALATION

In the United States, benzyl chloride is emitted to the atmosphere from its commercial production and use at a rate of 45,000 pounds/year (Anderson, 1983). These emissions originate from scrubber vents, vacuum jets, storage and fugitive emissions and equipment leaks.

Singh et al. (1982) collected ambient air samples from seven U.S. cities (Houston, St. Louis, Denver, Riverside, Staten Island, Pittsburgh and Chicago) to determine the atmospheric concentrations of 20 organic compounds. Ambient benzyl chloride concentrations as high as 110 ppt were measured, but in general, benzyl chloride was not detectable at 5 ppt levels. Benzyl chloride concentrations of 1-2 ppb were detected near the Stauffer Chemical plant in Edison, NJ (Singh et al., 1982). Air samples monitored in the Love Canal were reported to contain benzyl chloride, but no quantitative concentration values were given (Hauser and Bromberg, 1983).

Emissions of benzyl chloride from floor tile manufactured from butyl benzyl phthalate have been reported (Rittfeldt et al., 1983; Sandberg et al., 1984). Butyl benzyl phthalate is manufactured from benzyl chloride and may contain the chloride as an impurity. Benzyl chloride has also been detected in emissions resulting from the thermal oxidative degradation of polyvinyl chloride, neoprene and rigid urethane foam compounds (Hartstein and Forshey, 1974).

3.4. DERMAL

Pertinent data regarding dermal exposure to benzyl chloride could not be located in the available literature as cited in the Appendix. Dermal exposure is most likely to result from occupational environments involving the production and use of benzyl chloride.

3.5. SUMMARY

Benzyl chloride has been detected in industrial wastewater effluents (IARC, 1982), in Delaware River water (Sheldon and Hites, 1978), in sediment/soil/water from the Love Canal (Hauser and Bromberg, 1983), and in surface waters in a few areas of New Jersey (Pellizzari et al., 1979). The presence of benzyl chloride in these samples is attributed to industrial

release and dumping. The lack of monitoring data on benzyl chloride in water is consistent with the rapid degradation of benzyl chloride by hydrolysis.

Benzyl chloride is emitted to the atmosphere from industrial production and use sources at the rate of 45,000 pounds/year (Anderson, 1983). While low levels of benzyl chloride have been detected in urban air samples, the fact that it is not generally detected is consistent with its rapid degradation by OH• radicals in the atmosphere (Singh et al., 1982).

4. PHARMACOKINETICS

4.1. ABSORPTION

Following gavage dosing of male and female F344 rats with 25 mg/kg of [methylene- ^{14}C] benzyl chloride in corn oil, ~15-24% of the administered radioactivity was recovered in the urine at 3 hours (Bunner and Creasia, 1982). At 24 hours, 65-75% of the radioactivity was recovered in the urine. These data indicate that $\geq 65-75\%$ of benzyl chloride was absorbed from the gastrointestinal tract of rats and that absorption was rapid. In rabbits given a single oral dose of 2000 mg/kg benzyl chloride in water, 86% of the dose was recovered as ether soluble acid metabolites in the urine collected over 24 hours (Bray et al., 1958). Thus, benzyl chloride was extensively absorbed from the gastrointestinal tract of rabbits.

4.2. DISTRIBUTION

— Bunner and Creasia (1982) orally dosed rats with 25 mg/kg of [^{14}C]-benzyl chloride in corn oil to study the tissue distribution of radioactivity. The rats were killed at 3, 6 or 24 hours after administration. Radioactivity was detected in all tissues sampled at each time point. — Levels in the gastrointestinal tract, liver and kidneys were consistently higher than levels in blood at each sampling time. Radioactivity levels in the heart, stomach, lungs, fat, muscle and blood were highest at 3 hours. Although excretion of radioactivity was essentially complete at 24 hours, low levels were still detected in the organs and tissues at 24 hours.

4.3. METABOLISM

In rats (Barnes et al., 1959) and rabbits (Bray et al., 1958), oral administration of benzyl chloride led primarily to the formation of a mercapturic acid conjugate. Of the total doses administered, 27% was found as this conjugate in the urine of the rat and 49% in the urine of the

rabbit. Excretion of mercapturic acid conjugates was essentially complete in 24 hours for both species (Barnes et al., 1959; Bray et al., 1958). Conjugation is catalyzed by glutathione S-arylalkyltransferase (Boyland and Chasseaud, 1969). Glutathione levels in liver homogenates were reduced to 15% of control levels 6 hours after oral administration (Suga et al., 1966), indicating that conjugation occurred in the liver. Other metabolites of benzyl chloride detected in the urine of rabbits were a glycine conjugate (accounting for 20% of the dose) and a glucosiduronic acid [accounting for 0.4% of the dose (Bray et al., 1958)]. No benzilic acid or hippuric acid derivatives were detected as metabolites of benzyl chloride in the rabbit. Maitrya and Vyas (1970), however, detected an increased amount of hippuric acid in the urine of rats that were dosed orally with 44 mg/kg/day benzyl chloride for 7 days.

4.4. EXCRETION

Within 24 hours of oral administration of [^{14}C]-benzyl chloride to rats, 65-75% of the radioactivity isotope was recovered in the urine (Bunner and Creasia, 1982). Females excreted radioactivity at a significantly faster rate than males. The percentages of the dose of radioactivity recovered in the urine after 3, 6 and 24 hours were 14.9, 41.0 and 65.1%, respectively, in the males and 23.7, 54.7 and 74.4%, respectively, in the females. After 24 hours, ~15% of the radioactivity was recovered in the feces.

4.5. SUMMARY

Benzyl chloride was extensively absorbed from the gastrointestinal tract of rats and rabbits following oral dosing; ~70 and 86%, respectively, of the administered dose was recovered as metabolites in the urine collected over

24 hours (Bunner and Creasia, 1982; Bray et al., 1958). Following absorption, benzyl chloride was widely distributed to organs and tissues of rats (Bunner and Creasia, 1982). Although excretion of metabolites by rats (Bunner and Creasia, 1982) and rabbits (Bray et al., 1958) was essentially complete at 24 hours after dosing, radioactivity was still detectable in all organs and tissues of rats dosed with [^{14}C]-benzyl chloride (Bunner and Creasia, 1982). The main urinary metabolite of rats and rabbits was a mercapturic acid conjugate (Barnes et al., 1959; Bray et al., 1958), formed by conjugation of benzyl chloride with glutathione in the liver (Boyland and Chasseaud, 1969). Other urinary metabolites in rabbits were glycine conjugates and glucosiduronic acid conjugates (Bray et al., 1958). Increased amounts of hippuric acid were detected in the urine of rats after oral dosing with benzyl chloride (Maitrya and Vyas, 1970). At 24 hours after oral dosing with [^{14}C]-benzyl chloride, ~70% of the dose of radioactivity was detected in the urine and ~15% was detected in the feces of rats (Bunner and Creasia, 1982).

5. EFFECTS

5.1. CARCINOGENICITY

5.1.1. **Animal Studies.** A recently completed NCI bioassay (Lijinsky, 1985) concerning the carcinogenic potential of benzyl chloride has been made available as a prepublication manuscript. Fifty-two Fischer F344 rats and 52 B6C3F1 mice of each sex and species were administered benzyl chloride by gavage, in corn oil, 3 times/week for 104 weeks. There were no significant differences in survival between treated groups and controls. All surviving animals were sacrificed for comprehensive histopathological analysis 3-4 weeks after the last dose. All animals that died or were killed in extremis were also examined histologically, unless examination was precluded by autolysis. Equal numbers of vehicle-treated animals served as controls. The rats received either 0, 15 or 30 mg/kg/dose, whereas the mice received either 0, 50 or 100 mg/kg/dose.

In female rats, the only statistically significant increase in tumor incidence attributed to treatment involved thyroid C-cell neoplasms (Table 5-1). This result represents a statistically significant positive dose-related trend (Cochran-Armitage $p=0.007$), and a significant difference between the high-dose groups and control (Fischer Exact $p=0.009$). Lijinsky (1985) noted that the incidence of these neoplasms in treated females was higher than that seen in historical controls (~10%). Squamous cell papillomas were observed in the forestomachs of three high-dose male rats and in the oral cavity of one high-dose female rat; these lesions were not observed in controls. There were no other treatment-related neoplastic effects in rats.

The incidences of a variety of neoplasms were increased in benzyl chloride-treated mice (see Table 5-1). Male mice given the high dose had a significantly increased incidence of hemangioma/hemangiosarcoma ($p=0.028$),

TABLE 5-1

Incidence of Tumors in Rats and Mice Treated by Gavage with Benzyl Chloride (~98%) in Corn Oil for 104 Weeks and Observed for 3-4 Additional Weeks^a

Species/Strain	Sex	Dose ^b (mg/kg)	Target Organ	Tumor Type	Tumor Incidence ^c (p value)
Rat/Fischer 344	F	0	thyroid	C-cell adenoma/ carcinoma	4/52 (p=0.007) ^d
		15			8/51
		30			14/52 (p=0.009) ^e
Mouse/B6C3F1	M	0	circulatory system	hemangioma/ hemangiosarcoma	0/52
		50			0/52
		100			5/52 (p=0.028) ^e
		0	forestomach	carcinoma	0/51
		50			2/52
		100			8/52 (p=0.003) ^e
		0	forestomach	carcinoma/ papilloma	0/51 (p<0.001) ^f
		50			4/52
		100			32/52 (p<0.001) ^e
		0	liver	carcinoma/ adenoma	17/52
		50			28/52 (p=0.024) ^e
		100			20/51
	F	0	lung alveolus/ bronchial	carcinoma/ adenoma	1/52
		50			2/51
		100			6/51 (p=0.053) ^e
Mouse/B6C3F1	F	0	forestomach	carcinoma/ papilloma	0/52 (p<0.001) ^f
		50			5/50
		100			19/51 (p<0.001) ^e

TABLE 5-1 (cont.)

QUALITY OF EVIDENCE

Strength of Study: Sufficient number of animals for analysis of late-developing tumors. Benzyl chloride administered by a relevant route of exposure at two doses in both sexes of two species for animals' lifespan. Histological examination was comprehensive.

Overall Adequacy: Adequate

^aSource: Lijinsky, 1985

^bThe compound was administered 3 times/week.

^cExpressed as number of animals with tumors/number of animals examined microscopically

^dResult of Cochran-Armitage test for dose-related trend (Lijinsky, 1985)

^eFischer's Exact Test

^fCochran-Armitage test performed at SRC

forestomach carcinoma ($p=0.003$) and carcinoma/papilloma ($p<0.001$) of the forestomach. Low-dose males had a significantly increased incidence of hepatic carcinoma/adenoma ($p=0.024$), although the occurrence of this lesion was not statistically significantly greater in the high-dose males. High-dose females similarly had an increased incidence of forestomach carcinoma/papilloma ($p<0.001$) and a marginally increased incidence of alveolar/bronchiolar adenomas or carcinomas ($p=0.053$).

Fukuda et al. (1981) conducted two skin-painting studies on specific-pathogen-free ICR mice, using benzyl chloride dissolved in benzene. In the first study, 10 μL of benzyl chloride was administered to 3-week-old mice 3 times/week for 4 weeks, followed by 2 times/week until termination at ~40 weeks. In the second study, 2.3 μL of benzyl chloride diluted to 25 μL with benzene was applied to the backs of 7-week-old mice twice/week for 50 weeks. Controls received either 10 or 25 μL benzene for the respective treatment schedules. Mice in the second study were sacrificed at ~80 weeks. All mice were examined for neoplasia either at termination or when sacrificed in moribund condition. Of 11 treated mice in the first study, none had tumors. In the second study, 2/20 of the controls developed lung adenomas only, while 5/20 treated mice developed tumors, which included two lung adenomas and three skin carcinomas. Two of these skin carcinomas metastasized to the primary lymphatic organs, livers or kidneys. Despite lack of statistically significant differences in tumor incidence between treated and control mice, the authors considered benzyl chloride a weak carcinogen.

Two skin-painting studies were done in order to assess the potency of benzyl chloride as an initiator. Coombs (1982a) treated the shaved backs of 40 T.O. (Swiss-Webster derived Theiler's Original) mice with 1.0 mg benzyl

chloride in toluene. One week later 10 μ l croton oil in toluene was used as a promoter, and reapplied twice weekly thereafter. Negative (croton oil only) and positive (0.4 mg benzo[a]pyrene) controls were also used. The authors looked for the first appearance of papillomas, which subsequently grew in size. At 10 months, 8/19 of the benzo[a]pyrene-treated mice had skin tumors, whereas 0/37 of the benzyl chloride-treated mice were similarly affected.

In a second initiation-promotion test (Coombs, 1982b), Sencar mice were initiated by topical application of 10, 100 or 1000 μ g benzyl chloride in acetone, followed by twice weekly promotion by 12-O-tetradecanoyl-phorbol-13-acetate. Negative and positive (7,12-dimethylbenzanthracene) controls were also used. By 11 weeks all positive controls had skin tumors, whereas at 6 months ~20% of the treated mice showed similar changes. Further details were not provided in the brief report.

Ashby et al. (1982) studied the ability of benzyl chloride to act as a "complete carcinogen". Groups of 20 Swiss mice were treated topically with 100 μ g benzyl chloride in toluene twice weekly. Negative and positive (benzo[a]pyrene) control groups were included. After 7.5 months, 18/20 of the positive controls had skin tumors, whereas none of the negative controls or benzyl chloride-treated mice had tumors. The authors concluded that the study design was inadequate to clearly consider benzyl chloride a noncarcinogen.

As reviewed by NIOSH (1978), Druckrey et al. (1970) produced local sarcomas in BD-strain rats by weekly subcutaneous injection of benzyl chloride in peanut oil. These tumors were found in 3/14 rats given 40 mg/kg/week and 6/8 rats given 80 mg/kg/week for 51 weeks. The average induction time was 500 days. Metastases to the lung occurred only in the high-dose group.

- Groups of 20 strain A/Heston mice were injected intraperitoneally, 8-12 times over a 24-week period with benzyl chloride in tricaprylin (Poirier et al., 1975). The total doses to the mice were 4.7, 11.8 or 15.8 mmol/kg. Mice were sacrificed after the 24-week dosing period. There were no differences in pulmonary adenoma formation between treated mice and vehicle- or sham-injected controls.

5.1.2. Human Studies. Four cases of cancer were found among 41 workers employed from 1954-1972 in a benzoyl chloride manufacturing plant (Sakabe et al., 1976). The production of benzoyl chloride involves benzyl chloride as a reagent. Two of these cases, which were not used in the epidemiological analysis (Table 5-2) presumably because the subjects were still alive, were diagnosed as maxillary malignant lymphoma and squamous cell carcinoma of the bronchus. The other cases used in the analysis were of lung cancer; latency periods of 6-18 years elapsed before diagnosis. Both workers were in their mid-forties, were smokers and were exposed to toluene, benzal chloride and benzotrichloride. The number of expected tumors in the cohort of 41 exposed workers was 0.06, compared with the Japanese national rates for death from lung cancer in males (relative risk=33.3; $p=0.002$). The number of expected tumors in the total cohort of 147 exposed and nonexposed workers was 0.22 (relative risk=9.1; $p=0.02$). The four cases of cancer were thought to be related to exposure to one or more of the chemicals in the benzoyl production process. Two additional cases of lung cancer were reported among workers engaged in benzoyl peroxide and benzoyl chloride production (Sakabe and Fukuda, 1977). While no epidemiological analysis was performed, these additional cases support the conclusion that workers in benzoyl chloride production may experience increased risk of cancer.

TABLE 5-2

Lung Cancer in Workers Occupationally Exposed to Benzoyl Chloride^{a,b}

Size of exposed Population	Size of Control Population	Sex	Duration of Exposure (years)	Tumor Type	Number of Tumors Observed	Number of Tumors Expected	Relative Risk (p value) ^c
41 (benzoyl chloride workers only)	Japanese national mortality rates	M	6-15	histologically undefined	2	0.06	33.3 (p=0.002)
147 (all workers)	Japanese national mortality rates	M, F	6-15	histologically undefined	2	0.22	9.1 (p=0.02)

QUALITY OF EVIDENCE

Strengths of Study: Study attempts to relate observed values with expected values from the general population

Weaknesses of Study: Both individuals with cancer were smokers and were exposed to other carcinogenic chemicals, including benzotrchloride. A third case of lung cancer (squamous cell carcinoma of the bronchus) was not included in the analysis

Overall Adequacy: Limited

^aSource: Sakabe et al., 1976

^b - Level of exposure was not reported

^cThe p values were obtained from IARC (1982).

A mortality study of cancer incidence among factory workers exposed to chlorinated toluenes was reported by Sorahan et al. (1983). Of the total cohort consisting of 953 workers at a British organic chemical factory, 163 had been exposed to chlorinated toluenes. Of the 25 deaths in the group of 163, 5 were due to digestive system cancer and 5 to respiratory cancers (Table 5-3). Expected numbers were calculated from the mortality rates for England and Wales. Because of the association of cancer with benzotrichloride, as well as benzyl chloride, in animal studies, it is not possible to attribute the increased risk to either chemical alone.

Another retrospective mortality study of workers exposed to benzyl chloride, benzotrichloride and benzoyl chloride was conducted at a Velsicol Chemical Company chlorination plant (Wong and Morgan, 1984). The cohort consisted of 697 male workers who had been employed for <1 to >35 years. Analyses were based on U.S. mortality rates for males. There were no significant differences in either mortality or death rates from all cancers in the total cohort. While no cases of digestive system cancers were found, there were 7 cases of respiratory system cancer, compared with 2.84 expected cases in the total cohort; the SMR of 246.3 was not significant (Table 5-4). Five of the deaths from respiratory cancer occurred in workers employed for ≥ 15 years; compared with the 1.32 expected, the SMR of 379.5 was significant ($p \leq 0.05$). When the data were analyzed for the number of workers in jobs with potential exposure to benzyl chloride, benzoyl chloride or benzotrichloride, the number of tumors expected was 2.69 in each case and the SMR was significant for each case ($p \leq 0.05$). Since the majority of the workers fell into all three categories, it is not possible to determine the contribution of the individual chemicals to the increased risk of respiratory cancers. Other confounding factors included lack of smoking history data and the proximity of a coke plant to the plant under study.

TABLE 5-3
Digestive and Respiratory Cancers in Humans Occupationally Exposed to Chlorinated Toluenes*

Size of Exposed Population	Size of Control Population	Sex	Level of Exposure	Duration of Exposure	Target Organ	Tumor Type	Number of Tumors Observed	Number of Tumors Expected	Relative Risk (p value)
163	England and Wales mortality rates	M	1-10 ppm	6 months to >40 years	digestive system	cancer	5	1.24	SMR-403 (p<0.05)
					respiratory system	cancer	5	1.78	SMR-281 (p<0.05)
					digestive and respiratory systems	cancer	10	3.98	SMR-251 (p<0.01)

QUALITY OF EVIDENCE

Strengths of Study: Time- and age-specific comparisons between the exposed group and national mortality rates were made. Similar tumors were observed in laboratory rodent studies.

Weaknesses of Study: Exposure was to several chlorinated toluene compounds, so the cancers cannot be attributed to benzyl chloride exposure alone.

Overall Adequacy: Limited

*Source: Sorahan et al., 1983

TABLE 5 4

Respiratory System Cancers in Male Workers Employed at a Velsicol Chemical Chlorination Plant with Potential Exposure to Benzyl Chloride, Benzotrifluoride and Benzoyl Chloride^{a,b}

Size of Cohort	Duration of Exposure (years)	Number of Tumors Observed	Number of Tumors Expected	Relative Risk (p value)
697 (total cohort)	<1 to >35	7	2.84	SMR=246.3 (NS)
113	≥15	5	1.32	SMR=379.5 (p<0.05)
548	<15	2	1.52	SMR=131.2 (NS)
662 (number ever in jobs with potential exposure to benzyl chloride)	<1 to >35	7	2.69	SMR=259.9 (p<0.05)
670 (number ever in jobs with potential exposure to benzoyl chloride)	<1 to >35	7	2.69	SMR=259.9 (p<0.05)
669 (number ever in jobs with potential exposure to benzotrifluoride)	<1 to >35	7	2.69	SMR=260.1 (p<0.05)

TABLE 5-4 (cont.)

QUALITY OF EVIDENCE

Strengths of Study: Data for deaths from all cancer types and from particular cancer types were analyzed for the total cohort and for subcohorts broken down by job description, length of employment, analysis of latency, race and by exposure to specific chemicals. Analyses were based on United States mortality rates for males.

Weaknesses of Study: Relatively small cohort, data on cigarette smoking and other confounding factors were not obtained; other occupational and environmental exposures (a coke plant was adjacent to the study plant); levels of exposure not quantitated.

Overall adequacy: Limited

^aSource: Wong and Morgan, 1984

^bNumber of expected tumors were based on United States mortality rates for males.

NS = Not significant

5.2. MUTAGENICITY

Benzyl chloride was tested for its mutagenic activity in a variety of test systems as part of the United Kingdom Environmental Mutagen Society's (UKEMS) collaborative genotoxicity trial. 4-Chloromethylbiphenyl and 4-hydroxymethylbiphenyl were also evaluated as part of this trial. The mutagenicity data for benzyl chloride generated by the participating laboratories have been summarized in several reviews (Venitt, 1982; Parry and Wilcox, 1982; Scott, 1982; Arlett, 1982; Topham, 1982). In general, benzyl chloride appears to be a weak mutagen in a variety of prokaryotic and eukaryotic tests. It has been reported to produce gene mutations in bacteria, fungi, Drosophila and mammalian cells in culture. It is clastogenic and produces sister chromatid exchanges in Chinese hamster cells in vitro (Table 5-5). Mitotic recombination assays in fungi, DNA repair assays in bacteria, DNA and hemoglobin DNA binding assays also provide evidence for the genotoxicity of benzyl chloride. It should be emphasized, however, that the mutagenic activity of benzyl chloride is not consistently detected. Some laboratories have reported negative results (see Table 5-5). The mutagenicity testing of benzyl chloride is briefly summarized below and in Table 5-5.

5.2.1. Gene Mutation Studies.

5.2.1.1. BACTERIA -- Venitt (1982) summarized the bacterial mutation data on benzyl chloride from 11 different laboratories participating in the UKEMS collaborative study and concluded that benzyl chloride appears to be a weak mutagen only in Salmonella typhimurium TA100, which is a base-pair substitution sensitive strain that is also responsive to certain frameshift acting mutagens. Venitt emphasized that although most laboratories reported benzyl chloride to be weakly mutagenic on at least one occasion, the

TABLE 5-5
Mutagenicity Testing of Benzyl Chloride

Assay	Indicator/ Organism	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Bacterial reverse mutation	<u>Salmonella</u> <u>Lyphimurium</u> TA98, TA100, TA1535, TA1537, TA1538	plate assay	100-500 µg/plate	+/- S9	+/-	Slightly mutagenic to TA100 in presence of S9	Booth et al., 1983
	<u>S. typhimurium</u> TA98, TA100, TA1535, TA1537 TA1538	plate assay	31.25-4000 µg/plate	+/- S9	+/+	Weakly mutagenic in TA100 minus S9, in presence of S9 response is greatly enhanced	Brooks and Gonzalez, 1982a
	<u>S. typhimurium</u> TA98, TA100, TA1535, TA1537 TA1538	plate assay	7.81 µg/plate	+/- S9	-/-	Concentrations tested may have been too low to detect a muta- genic response	Jones and Richold, 1982
	<u>S. typhimurium</u> TA98, TA100, TA1535, TA1537 TA1538	urine assay	1100 mg/kg bw per os in male and female mice	+/- B- glucuronidase	-/-	NC	Jones and Richold, 1982
	<u>S. typhimurium</u> TA100	plate assay	1-1000 µg/plate	- S9	+	Weakly mutagenic	Kirkland et al., 1982a
	<u>S. typhimurium</u> TA98, TA100, TA1535, TA1537 TA1538	plate assay	50-400 µg/plate	+/- S9	?/-	Cytotoxic >400 µg/plate	Ladner, 1982
	<u>S. typhimurium</u> TA98, TA100, TA1535, TA1537 TA1538	plate test	31.2-1000 µg/plate	+/- S9	+/-	Weakly mutagenic to TA100 in a duplicate study in presence of S9	Varley, 1982
	<u>S. typhimurium</u> TA98, TA100, TA1535, TA1537 TA1538	plate test	1-5000 µg/plate	+/- S9	+/-	Dose-dependent increased number of revertants to TA100 with S9 (frequency of background rever- tants too low for TA100)	Watkins and Rickard, 1982
	<u>S. typhimurium</u> TA98, TA100,	fluctuation assay	1-20 µg/ml	+/- S9	+/+	Addition of S9 reduced mutagenicity	Booth et al., 1983

TABLE 5-5 (cont.)

Assay	Indicator/ Organism	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Bacterial reverse mutation	<u>S. typhimurium</u> TA98, TA100	fluctuation assay	1-250 µg/ml	NR	-	NC	Pour et al., 1982
	<u>S. typhimurium</u> TA98, TA100	fluctuation assay	0.1-250 µg/ml	+/- S9	-/-	NC	Sargent and Regnier, 1982
	<u>S. typhimurium</u> TA1535, TA1538	spot test	0.01-0.8 µg/plate	+/- S9	-/+	Weakly mutagenic to TA1535 in the absence of S9	Rosenkranz and Polier, 1979
	<u>S. typhimurium</u> TA98	fluctuation assay	5-150 µg/ml	+/- S9	+/+	NC	Styles and Pritchard, 1982
Bacterial DNA repair	<u>Escherichia</u> <u>coli</u> P3478	plate assay	25 µg	- S9	+	NC	Fluck et al., 1976
	<u>E. coli</u>	disk diffusion	10 µg	+ S9	+	NC	Rosenkranz and Lelher, 1980
	<u>E. coli</u>	liquid suspension	10 µg/ml	+/- S9	+	NC	Rosenkranz and Lelher, 1980
Mitotic gene conversion	<u>Saccharomyces</u> <u>cerevisiae</u>	plate assay	31.3-500 µg/ml	+/- S9	+/+	Conversion to His and Trp prototrophs positive only near cytotoxic doses	Brooks and Gonzalez, 1982b
	<u>S. cerevisiae</u>	plate assay	0.5-100 µg/ml	+/- S9	+/+	Cytotoxicity >90% at >50 µg/ml. More revertants in absence of S9.	Parry, 1982a
Mitotic crossing-over	<u>S. cerevisiae</u>	plate assay	25-200 µg/ml	+/- S9	+/+	NC	Parry, 1982b
Cytotoxicity	<u>S. cerevisiae</u>	plate assay	50-250 µg/ml	NR	+	Greatest cytotoxicity to a rad strain involved in excision repair	North and Parry, 1982
Chromosomal aneuploidy	<u>S. cerevisiae</u>	plate assay	25-200 µg/ml	+/- S9	-/-	NC	Parry, 1982b
Mitotic crossing-over	<u>Aspergillus</u> <u>nidulans</u>	plate assay	100-5000 µg/plate	+/- S9	-/-	A very slight induction of crossing-over when conidia were preincubated 5-6 hours	Watkins, 1982

TABLE 5-5 (cont.)

Assay	Indicator/ Organism	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Chromosomal aneuploidy	<u>A. nidulans</u>	plate test	100-5000 µg/plate	+/- S9	-/-	NC	Watkins, 1982
Reverse mutation	<u>Neurospora crassa</u>	In-plating	50-350 µg/ml	NR	+	NC	Luker, 1982
Forward mutation	<u>N. crassa</u>	In-plating	50-350 µg/ml	NR	+	NC	Luker, 1982
Sex-linked recessive lethal	<u>Drosophila melanogaster</u>	diet	4 mM	NA	-	Larval feeding	MacDonald and Telford, 1982
Somatic mutations	<u>D. melanogaster</u>	diet	0.5-2.0 mM	NA	+	Expression of red or white mosaic eye sectors	Fahmy and Fahmy, 1982
Sex-linked mutations	<u>D. melanogaster</u>	diet	2.0 mM	NA	+	NC	Fahmy and Fahmy, 1982
Sister chromatid exchange	CHO cells	In vitro; liquid medium	-7-20 µg/ml	- S9	+	NC	Phillips and James, 1982
Sister chromatid exchange	V79 cells	In vitro; liquid medium	-1-13 µg/ml	+/- S9	+/+	Similar response seen in CHO cells but not in human lympho- cyte culture	Scott, 1982
Unscheduled DNA repair	HeLa S3 cells	In vitro; liquid medium	10 ⁻¹⁰ to 10 ⁻⁸ M	+/- S9	-/-	NC	Booth et al., 1983
Unscheduled DNA synthesis	HeLa S3 cells	In vitro; liquid medium	10 ⁻⁷ to 10 ⁻⁸ M	+/- S9	-/-	NC	Barrett, 1982
Unscheduled DNA synthesis	HeLa S3 cells	In vitro; liquid medium	5x10 ⁻⁸ to 10 ⁻² M	NR	+	Authors claimed DNA repair syn- thesis at 5x10 ⁻⁸ to 5x10 ⁻⁴ M, but no background counts given	Schliffmann et al., 1983
Unscheduled DNA synthesis	WI-48 cells	In vitro; liquid medium	10 ⁻⁶ to 10 ⁻² M	- S9	-	DNA counts for benzyl chloride at 10 ⁻⁶ M were 1.7 times those of negative controls; positive control at 10 ⁻⁸ M was 24.7 times negative control	Mitchell, 1976
DNA strand breaks	A549 cells	In vitro; liquid medium	125-500 µg/ml	none	+	NC	Mirzayans et al., 1982a

TABLE 5-5 (cont.)

Assay	Indicator/ Organism	Application	Concentration or Dose	Activating System	Response	Comment	Reference
Cellular morphological transformation	Syrian hamster embryo cells	<u>In vitro</u> ; liquid medium	0.1-100 $\mu\text{g}/\text{ml}$	none	+	Cellular transformation at 0.1, 1, 10 $\mu\text{g}/\text{ml}$	Plenta, 1980
Gene mutation	mouse lymphoma L5178Y cells	<u>In vitro</u> ; liquid medium	up to 20 $\mu\text{g}/\text{ml}$	+/- S9	-/?	Questionable mutagenic response in the absence of S9	Ross and MacGregor, 1982
Gene mutation	CHO cells	<u>In vitro</u> ; liquid medium	10-50 $\mu\text{g}/\text{ml}$	none	+	Lack of dose-response relation- ship may be due to lethality at higher doses	Phillips and James, 1982
Gene mutation	8-Azag resist- ance in V79	<u>In vitro</u> ; liquid medium	80-200 μM	none	+	Dose-response relationship was apparent	Mirzayans et al., 1982b
Gene mutation	8-Azag resist- ance in V79	<u>In vitro</u> ; liquid medium	10.3-25.1 $\mu\text{g}/\text{ml}$	S9	+	The authors concluded that there was a positive response	Lee and Webber, 1982
Chromosomal aberration	CHO cells	<u>In vitro</u> ; liquid medium	10-35 $\mu\text{g}/\text{ml}$	none	+	NC	Phillips and James, 1982
DNA repair	CHO cells	<u>In vitro</u> ; liquid medium	25 $\mu\text{g}/\text{ml}$ (lowest effective concentration)	none	+	Slightly mutagenic to DNA excision repair-deficient strains but not mutagenic to DNA strand breaking-rejoining deficient strain	Hoy et al., 1984
Chromosomal aberration	human lymphocytes	<u>In vitro</u> ; liquid medium	2.5-10 $\mu\text{g}/\text{ml}$	NR	-	Measured gaps, breaks, rearrangements and numerical aberrations	Kirkland et al., 1982b
Sperm head abnormality	CBA x BALB/C F ₁ mice	<u>In vivo</u> ; subcutaneous	125-1000 mg/kg	NA	+	Increase in abnormalities only at doses which were lethal	Scott and Topham, 1982
Micronucleus test	mice	<u>In vivo</u> ; intraperi- toneally	75-1200 mg/kg (total dose)	NA	-	NC	Danford and Parry, 1982
Micronucleus test	SPF NMRI mice	<u>In vivo</u> ; per os	25-400 mg/kg (2 times)	NA	-	NC	Hartley-Asp, 1982

NR = Not reported; NA = not applicable; NC = no comment

positive results were not always reproducible. A few laboratories found that the induced increases in revertants did not require exogenous metabolic activation (Kirkland et al., 1982; Brooks and Gonzalez, 1982a). This finding is not unexpected since benzyl chloride is a direct DNA alkylating agent (Wallis, 1981). Although benzyl chloride may be a direct acting mutagen, one study reported a higher mutagenic response in the presence of liver S9 activation compared with the response in the absence of S9 mix (Brooks and Gonzalez, 1982), whereas other studies found that benzyl chloride was only weakly mutagenic in Salmonella TA100 in the presence of S9 liver activation (Booth et al., 1983; Varley, 1982; Watkins and Richard, 1982). Thus, benzyl chloride may be metabolized to a mutagenic intermediate(s). Still other laboratories questioned whether benzyl chloride was mutagenic at all in the Salmonella test with or without S9 activation (Ladner, 1982; Jones and Richold, 1982).

In bacterial fluctuation tests using Salmonella, benzyl chloride has been reported to elicit positive responses, questionable positive responses, or to be negative (Styles and Pritchard, 1982; Pour et al., 1982; Sargent and Regrier, 1982).

Venitt (1982) also assessed the bacterial data for Escherichia coli and concluded that benzyl chloride was weakly mutagenic in E. coli WP2uvrA(p) in the absence of S9 mix. Venitt further concluded, albeit from limited data, that E. coli is slightly more sensitive to the mutagenic action of benzyl chloride than Salmonella. E. coli WP2, Salmonella TA100, is reverted by base-pair substitution mutagens.

5.2.1.2. FUNGI -- Parry and Wilcox (1982) summarized the mutagenicity testing of benzyl chloride in fungi in a report of the UKEMS collaborative trial. Luker (1982) found that benzyl chloride produced forward and reverse

gene mutations in Neurospora crassa. Parry and Wilcox (1982) reported that benzyl chloride caused mutations at the leu and lys loci in Saccharomyces. These loci are sensitive to base-pair substitution acting mutagens; a result similar to that found in the bacterial testing.

5.2.1.3. DROSOPHILA -- Topham (1982) reviewed the Drosophila UKEMS collaborative studies. MacDonald and Telford (1982) tested benzyl chloride (10 mg in 1 ml 5% DMSO) in Drosophila melanogaster by larval feeding. Although no increase in the frequency of sex linked recessive lethals (SLRLs) was found, the sample size tested was too small to detect weak mutagenic activity. In addition, not all germ cell stages were adequately evaluated. Fahmy and Fahmy (1982) reported that benzyl chloride induced both germinal (judged to be weakly active for SLRLs) and somatic mutations in male Drosophila.

5.2.1.4. MAMMALIAN CELLS IN CULTURE -- Arlett (1982) reviewed the test results of benzyl chloride in mammalian cells generated under the auspices of the UKEMS collaborative genotoxicity trial. In 3 of 4 studies, benzyl chloride was found to be mutagenic. Briefly, positive results were reported for Chinese hamster V79 cells (8-AzaG) and for Chinese hamster ovary cells (6-TG) in the presence or absence of S9 activation (Lee and Webber, 1982; Mirzayans et al., 1982; Phillips and James, 1982). Although a weak increase (not quite 2-fold the spontaneous frequency) in mutants was found in the absence of S9 activation for the mouse lymphoma L5178Y test, a negative response was concluded; in the presence of S9 mix, no increase in mutant colonies was found (Ross and McGregor, 1982).

5.2.2. Cytogenetic Studies.

5.2.2.1. **MAMMALIAN CELLS** -- The UKEMS collaborative studies on the cytogenetic tests of benzyl chloride were summarized by Scott (1982) and Topham (1982). Benzyl chloride induced chromosomal aberrations in cultured Chinese hamster ovary cells (Phillips and James, 1982) and in cultured rat-liver epithelial cells (Dean and Hodson-Walker, 1979) and caused mitotic inhibition in human peripheral lymphocytes at low doses (Kirkland et al., 1982). At noninhibitory doses, benzyl chloride gave negative results for chromosomal aberrations. Benzyl chloride was reported to produce an increase in polyploid cells but not aneuploid cells (i.e., numerical chromosomal changes) of Chinese hamster ovary cells. The increase in polyploidy may be the result of a lesser effect of benzyl chloride inhibition on the proliferation of existing polyploid cells than on diploid cells. Benzyl chloride did not produce aneuploidy or polyploidy in rat-liver epithelial cells or human lymphocytes.

Sister chromatid exchange induction by benzyl chloride was reported in cultured Chinese hamster ovary and V79 fibroblast cells without liver S9 activation (Scott, 1982; Phillips and James, 1982). Benzyl chloride produced a strong dose-related response.

Danford and Parry (1982) tested the ability of benzyl chloride to induce chromosomal aberrations in vivo. Mice were given two i.p. injections of 300 mg/kg benzyl chloride. There were no significant increases in micronuclei in the bone marrow cells. Topham (1982) indicated that benzyl chloride gave negative results in mouse micronuclei tests using two other routes of exposure, namely subcutaneous and oral.

5.2.2.2. **FUNGI** -- Benzyl chloride did not produce aneuploidy in fungal cultures (Parry and Wilcox, 1982).

5.2.3. Other Studies Indicative of DNA Damage.

5.2.3.1. YEAST -- Benzyl chloride has been reported to induce mitotic crossing over in both Saccharomyces cerevisiae and Aspergillus nidulans (Watkins, 1982; Brooks and Gonzalez, 1982; Parry, 1982a,b). Benzyl chloride was also found to induce mitotic gene conversion in yeast (Wilcox and Parry, 1982; Brooks, 1982).

5.2.3.2. BACTERIA -- Benzyl chloride was found to cause differential growth inhibition in the E. coli PolA assay (Rosenkranz and Leifer, 1980; Fluck et al., 1976).

In assays of unscheduled DNA synthesis and repair (Mitchell, 1976; Barrett, 1982; Booth et al., 1983; Schiffmann et al., 1983), benzyl chloride was generally ineffective in the dose range 10^{-10} to 10^{-2} M. Mirzayans and Wales (1985), Mirzayans et al. (1982) and Schiffmann et al. (1983) reported that the compound increased unscheduled DNA synthesis in the dose range 5×10^{-5} to 5×10^{-4} M in human alveolar tumor cells, human XP fibroblasts. Arlett concluded that although Mirzayan et al. and Barrett are contradictory, the authors were looking at different endpoints.

In CBAxBALB/C mice, benzyl chloride induced increases in sperm head abnormalities only at lethal doses (Scott and Topham, 1982).

Murzayan et al. (1982) tested cultured human alveolar tumor cells, A549, for DNA damage and repair as well as inhibition of cell growth using benzyl chloride concentrations of 125, 250 and 500 $\mu\text{g}/\text{mL}$ for DNA tests and ~30-100 $\mu\text{g}/\text{mL}$ for the growth inhibition tests (estimated from graph). DNA strand breaks were increased in a dose-dependent manner. The repair of this damage could be inhibited by ara c. Cell growth was also inhibited in a dose-dependent manner.

5.3. TERATOGENICITY

In the only available report of the teratogenic and fetotoxic effects of benzyl chloride exposure, five groups of 20 female Wistar rats were gavaged from days 1-19 of gestation with 0, 0.00006, 0.0006, 0.006 or 208 mg/kg/day benzyl chloride in sunflower oil (Leonskaya, 1980). Dams were sacrificed on day 20 for assessment of fetotoxicity and teratogenicity. "Embryonal mortality" (not otherwise specified) was 53.4% at the highest dose, compared with 11.6% in controls. Leonskaya (1980) reported that the rats given the two intermediate doses had a statistically significant increase in embryonal mortality, although no supporting data were provided. In a review of this study by Rudnev et al. (1979), it appeared that 0.00006 mg/kg/day was the only dose that did not affect the craniocaudal index. Wavy ribs occurred in 1/58 and 4/70 fetuses at 0.0006 and 0.006 mg/kg/day, respectively; wavy ribs were not observed at 208 mg/kg/day, probably because of the high mortality (Leonskaya, 1980). In another experiment, Leonskaya (1980) treated groups of seven female rats with benzyl chloride in sunflower oil by gavage at 0, 0.00006 or 208 mg/kg/day on days 1-19 of gestation. The dams were allowed to deliver and the pups were observed for 1 month after birth. At 208 mg/kg/day, there was increased mortality and delayed development of the pups.

5.4. OTHER REPRODUCTIVE EFFECTS

In the study by Leonskaya (1980) (see Section 5.3.), some of the progeny of the rat dams that were treated with benzyl chloride during gestation were mated. Increased embryonal mortality was observed in the second generation of the 208 mg/kg/day group.

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5.5. CHRONIC AND SUBCHRONIC TOXICITY

In the chronic NCI bioassay (see Section 5.1.), 52 male and 52 female rats were administered 0, 15 or 30 mg/kg/dose benzyl chloride, 3 times/week for 104 weeks (Lijinsky, 1985). Similarly, 52 male and 52 female mice were given 0, 50 or 100 mg/kg/dose, 3 times/week for 104 weeks. All administrations were by gavage, and the benzyl chloride was suspended in corn oil. Lijinsky (1985) found no treatment-related non-neoplastic effects in rats; however, mice that did not have tumors exhibited treatment-related epithelial hyperplasia of the stomach. It was unclear whether this effect was also dose-related.

Lijinsky (1985) also conducted a subchronic study on B6C3F1 mice (10/sex/dose), in which doses of 0, 6.3, 12.5, 25, 50 or 100 mg/kg benzyl chloride in corn oil were given by gavage, 3 times/week. Male mice were dosed for 36 weeks and females for only 26 weeks. The only effect observed was moderate to severe liver hyperplasia at all doses.

Groups of 10 male and 10 female 8- to 10-week-old Fischer 344/N, rats were treated by gavage with 0, 15, 30, 62, 125 or 250 mg/kg of [^{14} C]-benzyl chloride in corn oil 3 days/week (Bunner and Creasia, 1982; Lijinsky, 1985). At the end of the study (37 weeks for males, 27 weeks for females), all surviving animals were sacrificed and necropsied for histopathological examination. The females were more sensitive to the toxic effects of benzyl chloride; a single dose of 250 mg/kg or four doses of 125 mg/kg killed all members of these groups and 62 mg/kg was fatal to 6/10 females by the end of the study. For the males, however, deaths did not occur until after five doses of 250 mg/kg or 6-9 doses of 125 mg/kg were administered. Among the histopathological findings in the rats that died were severe acute gastritis and ulceration of the squamous portion of the

stomach and a reduction of mucosal hyperplasia of the duodenum. Rats treated with ≥ 15 mg/kg had hyperkeratosis and/or hyperplasia of the squamous stomach and hyperplasia and focal necrosis of the heart.

Rudnev et al. (1979) administered doses of 0, 0.6, 0.06 and 0.006 mg/kg/day benzyl chloride in corn oil to groups of 15 rats of an unspecified strain and sex for 6 months. At the highest dose only there were increases in the concentration of blood inorganic phosphate and changes in the activities of alkaline phosphatase, cholinesterase and succinic dehydrogenase. No other details were given.

5.6. OTHER RELEVANT INFORMATION

Table 5-6 provides information on the acute toxicity of benzyl chloride in animals. Oral LD_{50} s range from 625-1231 mg/kg in rats and 780-1624 mg/kg in mice (Rudnev et al., 1979; Back et al., 1972), whereas the 2-hour inhalation LC_{50} s were reported to be 390 mg/m³ in mice and 740 mg/m³ in rats (Mikhailova, 1965). Despite these lethal concentrations, Back et al. (1972) reported that all rats and mice survived a 1-hour exposure to a 2000 mg/m³ concentration of benzyl chloride vapors. In the absence of additional experimental details, the reason for this discrepancy is unknown. Mikhailova (1965) placed a separate group of 10 white rats in an inhalation chamber and exposed them to 100 mg/m³ benzyl chloride for 2 hours. During a 1-month follow-up period, the treated rats showed a failure to gain weight compared with untreated controls. Hematological parameters were not affected. At concentrations >100 mg/m³, both rats and mice showed mucosal irritation, signs of excitement and slowed respiration. At 1000 mg/m³, nervous system effects, including motor automatism (mice) and neuromuscular twitching (rats), predominated.

TABLE 5-6
Acute Toxicity of Benzyl Chloride in Rats and Mice

Species	Route	LD ₅₀ or LC ₅₀	Reference
Rat	oral	625 mg/kg bw	Rudnev et al., 1979
	oral	1231 mg/kg bw	Back et al., 1972
	Inhalation	740 mg/m ³ (2 hours)	Mikhailova, 1965
Mouse	oral	780 mg/kg bw	Rudnev et al., 1979
	oral	1624 mg/kg bw	Back et al., 1972
	Inhalation	390 mg/m ³ (2 hours)	Mikhailova, 1965

Smyth (1956) reported that the only important effect of benzyl chloride inhalation in humans was irritation, which was said to predominantly affect mucous membranes and induce pulmonary edema. Mikhailova (1971) studied production workers exposed to ≥ 10 mg/m³ benzyl chloride vapors and recorded complaints of headaches, weakness, irritability, insomnia, tremors and poor proprioception. Aberrations in serum protein, bilirubin and leukocyte levels were observed, suggesting liver dysfunction. Mikhailova (1971) noted that at 160 mg/m³ benzyl chloride was unbearably irritating; 50-100 mg/m³ caused tearing and 5 minutes of exposure to 6-8 mg/m³ resulted in conjunctivitis in man. More specific details were not available. A human odor threshold of 0.24 mg/m³ for benzyl chloride was determined by Leonardoes et al. (1969). Key et al. (1982) reported incidences of contact dermatitis in workers occupationally exposed to benzyl chloride.

The sensitization characteristics of benzyl chloride were studied by Laudsteiner and Jacobs (1936), who intracutaneously injected the compound into guinea pigs twice weekly for 12 weeks. The guinea pigs were challenged with an unspecified test solution 2 weeks later. Erythema and swelling were apparently observed in response to the challenge. Rudnev et al. (1979) gave groups of 10 white rats oral doses of 0 (untreated and sunflower oil vehicle control groups), 0.00006, 0.0006 or 0.006 mg/kg. Three tests of immunocompetence, including a complement fixation assay, an indirect basophilic degranulation test and an autohemolysis patch test, were assessed before the start of experimentation and at 0, 4 and 8 weeks after the study ended. A liver extract from separate donor animals dosed for 30 days with benzyl chloride was used as test antigen. Rudnev et al. (1979) found that 0.0006 mg/kg was the minimum sensitizing dose for all three tests.

Fiala et al. (1982) described hepatic enzyme activity in rats given benzyl chloride in one or two large doses by an unspecified route. A large increase in γ -glutamyl transferase activity and a consequent feedback inhibition of reduced glutathione were noted. The authors stated that both of these events were necessary for the expression of rat liver carcinogenesis, but did not elaborate further. Walles (1981) observed that the degree of DNA alkylation in mouse testis and brain was elevated (relative to the degree of alkylation of hemoglobin) 1 hour after intravenous injection. After 24 hours, lung tissue showed an increased amount of alkylation.

The in vitro effects of benzyl chloride on DNA damage and repair have been studied by several authors. Benzyl chloride at 125 or 250 $\mu\text{g}/\text{ml}$ caused single strand breaks when incubated with cultured human alveolar tumor (A549) cells (Mirzayans et al., 1982); however, the effect was reversible (damage was fully repairable) 4 hours after treatment. Mirzayans and Waters (1985) studied the capacity of excision-deficient human fibroblasts to repair benzyl chloride-induced DNA damage. Unlike damage caused by UV light, benzyl chloride-induced damage was only marginally greater in the repair-deficient fibroblasts than in repair-proficient A549 cells. This result led the authors to conclude that benzyl chloride affected only the DNA damage rather than the cell's ability to repair such damage. In a study of cytotoxicity, benzyl chloride at 50 and 100 ppm was added to cultures of ELD ascites tumor cells (Holmberg and Malmfors, 1974a). Samples for estimation of the frequency of injured cells were then taken every 1/2 hour for 5 hours. The percentage of dead cells ranged from 3 (at incubation) to 11% (5 hours postincubation) for the 50 ppm group and 5 (at incubation) to 14.5% (5 hours postincubation) for the 100 ppm group. Control values ranged from 2.3-4.2%.

Holmberg and Malmfors (1974b) studied the in vitro mechanical response of mouse vas deferens tissue transmurally (electrically) stimulated in the presence of benzyl chloride. The compound produced a marked ability to potentiate this response and slightly inhibited norepinephrine uptake. In another experiment, Holmberg and Malmfors (1974b) attempted to elicit the response by exogenous norepinephrine, after tissue norepinephrine levels had been depleted by application of 6-hydroxydopamine. Application of 100 ppm benzyl chloride to this denervated preparation had little effect on the mechanical response; however, the concentration used may also have led to irreversible damage to smooth muscle cells. De Ceaurriz et al. (1983) found statistically significant and dose-related decreases in immobility in a "behavioral despair" swim test in Swiss OF1 mice exposed by inhalation to 0-22 ppm benzyl chloride.

5.7. SUMMARY

A recent 2-year NCI bioassay (Lijinsky, 1985) has provided convincing evidence of the carcinogenic potential of benzyl chloride in mice treated by gavage with 50 or 100 mg/kg/day, 3 days/week. Dose-related increases in the incidences of forestomach carcinomas and carcinomas/papillomas in both sexes were observed. Treated male mice had increased incidences of liver and circulatory system tumors, whereas high-dose females showed a marginally increased occurrence of pulmonary adenomas/carcinomas. Female rats treated with 15 or 30 mg/kg/day, 3 days/week had a dose-related increased incidence of C-cell adenoma/carcinoma of the thyroid. Humans studies (Sakabe et al., 1976; Sakabe and Fukuda, 1977; Sorahan et al., 1983; Wong and Morgan, 1984) have shown that occupational exposure to halogenated intermediates in benzoyl chloride production may increase the risk of respiratory cancer-induced mortality.

Benzyl chloride was weakly mutagenic to bacterial strains Salmonella typhimurium TA100 and Escherichia coli WP2 μ vr A(p), which are sensitive to the induction of point mutations (Venitt, 1982). It also expressed genotoxicity toward repair-deficient strains (Fluck et al., 1976; Rozenkranz and Leifer, 1980). Parry and Wilcox (1982) reported that benzyl chloride affects the replicative and repair mechanisms in fungi. In Drosophila melanogaster, benzyl chloride was found to induce somatic mutations more readily than sex-linked alterations (Fahmy and Fahmy, 1982). In mammalian culture, benzyl chloride was slightly mutagenic to DNA excision-repair deficient strains of CHO cells (Hoy et al., 1984), but was generally ineffective in altering unscheduled DNA synthesis (Mitchell, 1976; Booth et al., 1983). Scott and Topham (1982) concluded that benzyl chloride was generally not mutagenic in in vivo mammalian systems, including the mouse micronucleus and sperm head abnormality tests.

Leonskaya (1980) found that an oral dose of 208 mg/kg/day on days 1-19 of gestation in rats led to increases in embryonic mortality and developmental defects in surviving fetuses. Doses of 0.0006 and 0.006 mg/kg/day were reported to increase embryonic mortality and induce a slightly increased incidence of wavy ribs, although no supporting data for the former statement were provided. A dose of 0.00006 mg/kg/day was without effect.

Gavage administration of benzyl chloride in rats at 0.6 mg/kg/day for 6 months led to changes in serum enzymes and whole blood inorganic phosphate levels (Rudnev et al., 1979). Oral doses of 250 and 125 mg/kg benzyl chloride, 3 times/week were rapidly fatal to rats (Bunner and Creasia, 1982; Lijinsky, 1985). At ≥ 15 mg/kg, rats had hyperkeratosis and/or hyperplasia of the squamous stomach and hyperplasia and/or focal necrosis of the heart.

Lijinsky (1985) also treated male and female mice by gavage 3 times/week with benzyl chloride for 6-8 months. Doses of 125 and 250 mg/kg were fatal to all rats, whereas the mice exposed to the highest dose (100 mg/kg) survived. In mice, the only treatment-related pathological effect was hepatic hyperplasia. Rats treated with the highest doses had severe chronic gastritis and myocardial damage. Females were more sensitive to the gastric effects of benzyl chloride administration; at both 30 and 62 mg/kg, most of these rats had forestomach hyperplasia and/or hyperkeratosis. In a subsequent 2-year bioassay, Lijinsky (1985) observed no non-neoplastic effects at oral doses of up to 30 mg/kg/day benzyl chloride for 3 days/week in rats. Mice not otherwise afflicted with forestomach tumors showed forestomach hyperplasia at 50 or 100 mg/kg/day, 3 days/week.

Oral LD₅₀ values in rats, mice and rabbits after acute benzyl chloride administration range from 625-1624 mg/kg (Rudnev et al., 1979; Back et al., 1972). A 2-hour inhalation exposure to 100 mg/m³ caused inhibition in weight gain in 10 white rats (Mikhailova, 1965); higher doses caused mucosal irritation, delayed respiration and nervous system manifestations. An occupational study suggested that short exposures to as little as 6-8 mg/m³ are dangerous to mucous membranes (Mikhailova, 1971). At least two studies (Laudsteiner and Jacobs, 1936; Rudnev et al., 1979) have demonstrated the sensitization potential of benzyl chloride in rodents. Fiala et al. (1982) observed feedback inhibition of glutathione as a result of increased γ -glutamyl transferase activity after benzyl chloride administration. The degree of DNA alkylation in mouse testes and brain was significantly elevated over hemoglobin levels 1 hour after intravenous injection of benzyl chloride (Wallis, 1982).

6. AQUATIC TOXICITY

6.1. ACUTE

The available information concerning the acute toxicity of benzyl chloride to fishes is summarized in Table 6-1. LC_{50} values for the golden orfe, zebrafish and fathead minnow range from 3-16 mg/l (Curtis et al., 1979; Juhnke and Luedemann, 1978; Wellens, 1982). The most sensitive species tested may be the rainbow trout, Salmo gairdneri since 5 mg/l caused mortality in 12 hours (Applegate et al., 1957); however, the presentation of the results in this manner makes comparison with LC_{50} values difficult.

There is little information available concerning the acute toxicity of benzyl chloride to aquatic invertebrates (Table 6-2). Bringmann and Kuehn (1977, 1982) reported an EC_{50} for immobilization of 1.3 mg/l and a 24-hour LC_{50} of 8.4 mg/l for Daphnia magna. In the only study available involving a marine invertebrate, Curtis et al. (1979) reported a 96-hour LC_{50} for Penaeus setiferus of 3.9 mg/l, based on nominal concentrations. Based on actual measured concentrations of benzyl chloride in water, however, the 96-hour LC_{50} was 0.74 mg/l. The measured concentrations were lower than the nominal concentrations because benzyl chloride reacted with water to form hydrochloric acid and benzyl alcohol; this did not lower the pH to a toxic level (Curtis et al., 1979). Because benzyl chloride is unstable in water it is difficult to predict the effects of ambient concentrations since most toxicity data are based on nominal concentrations.

6.2. CHRONIC

Pertinent data regarding the chronic toxicity of benzyl chloride to aquatic organisms could not be located in the available literature as cited in the Appendix.

TABLE 6-1
Acute Toxicity of Benzyl Chloride to Fishes

Species	Concentration (mg/l)	Response	Reference
Golden orfe <u>Leuciscus idus</u>	0.6-11.3 3.0-16.0 5.5-22.6	48-hour LC ₀ 48-hour LC ₅₀ 48-hour LC ₁₀₀	Juhnke and Luedemann, 1978; Wellens, 1982
Zebrafish <u>Brachydanio rerio</u>	2.8 4.0 5.7	96-hour LC ₀ 96-hour LC ₅₀ 96-hour LC ₁₀₀	Wellens, 1982
Fathead minnow <u>Pimephales promelas</u>	11.6 7.3 4.7-7.8	24-hour LC ₅₀ 48-hour LC ₅₀ 96-hour LC ₅₀	Curtis et al., 1979
Rainbow trout <u>Salmo gairdneri</u>	5.0	Lethal in 12 hours	Applegate et al., 1957
Bluegill <u>Lepomis macrochirus</u>	5.0	Signs of distress in 15 minutes, but no mortality in 24 hours	Applegate et al., 1957
Sea lamprey <u>Petromyzon marinus</u>	5.0	No effect in 24 hours	Applegate et al., 1957
Aholehole <u>Kuhlia sandvicensis</u> <u>Trutta iridea</u>	1.0 10.0 10.0	No effect Irritant response Paralysis	Hiatt et al., 1953 Meinck et al., 1970
Carp <u>Cyprinus carpio</u>	17.0	Paralysis	Meinck et al., 1970

TABLE 6-2
Acute Toxicity of Benzyl Chloride to Invertebrates

Species	Concentration (mg/l)	Response	Reference
Water flea <u>Daphnia magna</u>	0.66 1.3 5.0 2.4 8.4 25.0	EC ₀ - immobilization EC ₅₀ - immobilization EC ₁₀₀ - immobilization 24-hour LC ₀ 24-hour LC ₅₀ 24-hour LC ₁₀₀	Bringmann and Kuehn, 1982 Bringmann and Kuehn, 1977
Protozoan <u>Entosiphon sulcatum</u>	25.0	toxicity threshold - inhibition of cell multiplication	Bringmann and Kuehn, 1980
White shrimp <u>Penaeus setiferus</u>	7.1 4.4 3.9 0.14	24-hour LC ₅₀ , based on nominal concentrations 48-hour LC ₅₀ , based on nominal concentrations 96-hour LC ₅₀ , based on nominal concentrations 96-hour LC ₅₀ , based on measured concentrations	Curtis et al., 1979

6.3. PLANTS

Bringmann and Kuehn (1978) reported toxicity thresholds for inhibition of cell multiplication in the blue-green algae, Microcystis aeruginosa (30 mg/l) and the green algae Scenedesmus quadricauda (50 mg/l). Bringmann and Kuehn (1976) reported the toxicity threshold in the bacterium, Pseudomonas putida to be 4.8 mg/l.

6.4. RESIDUES

Pertinent data regarding residues of benzyl chloride in aquatic biota could not be located in the available literature as cited in the Appendix.

6.5. SUMMARY

The available information concerning toxicity of benzyl chloride to aquatic organisms is limited. LC_{50} values for three fish species are 3-16 mg/l (see Table 6-1). The lowest nominal concentration at which adverse effects were reported was 1.3 mg/l, the EC_{50} for immobilization of Daphnia magna (Bringmann and Kuehn, 1982).

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

OSHA has established a workplace permissible exposure limit of 1 ppm or ~5 mg/m³ for benzyl chloride (CFR, 1985). Based upon the report (Mikhailova, 1971) that exposure to 6-8 mg/m³ benzyl chloride can induce mild conjunctivitis, NIOSH (1978) recommended a 15-minute ceiling concentration of 5 mg/m³. A recommended 8-hour TWA concentration of 1-3 mg/m³ was believed to be low enough to reduce the potential for long-term human health effects. Based on these data and the results of Smyth (1956), the ACGIH (1980) proposed a TLV of 5 mg/m³, which was adopted by the ACGIH (1985). Smyth (1956) had earlier reported that the established 5 mg/m³ threshold limit was "undoubtedly low enough to prevent lung injury." The Soviet standard for an 8-hour occupational exposure to benzyl chloride is 0.1 ppm (0.5 mg/m³) (U.S. EPA, 1980a).

7.2. AQUATIC

Pertinent data regarding aquatic guidelines and standards for benzyl chloride could not be located in the available literature as cited in the Appendix.

B. RISK ASSESSMENT

Parenteral and/or topical administration of benzyl chloride to laboratory animals has been shown to induce local, and occasionally metastatic, tumors (Druckrey et al., 1970; Coombs, 1982a,b). In none of these studies, however, was benzyl chloride considered more than a weak carcinogen. Other authors (Poirier et al., 1975; Fukuda et al., 1981; Ashby et al., 1982) have found no significant differences in tumor incidence between control and treated animals. The studies by Coombs (1982a,b) and Ashby et al. (1982) suggest that, when applied topically, benzyl chloride acts as a tumor initiator; however, since there are many strain, dose and methodology differences between these studies, generalizations about the carcinogenic potential of benzyl chloride are difficult. Moreover, in none of the studies was a treatment period of 2 years allowed for assessment of late tumorigenesis. Despite limitations in methodology in these early animal studies, IARC (1982) considered benzyl chloride a weak carcinogen.

Workers exposed occupationally to the intermediates in benzoyl chloride production showed increases in respiratory and digestive system cancers (Sorahan et al., 1983; Wong and Morgan, 1984; Sakabe et al., 1976; Sakabe and Fukuda, 1977). Because of small sample sizes, lack of data on cigarette smoking and the fact that exposure was to a mixture of halogenated intermediates, these data are of little value in determining the threat to human health of benzyl chloride exposure.

A more complete analysis of the carcinogenic potential of benzyl chloride was provided by the chronic bioassay by Lijinsky (1985). Male and female F344 rats and B6C3F1 mice were orally exposed to benzyl chloride in

corn oil, 3 times/week for 2 years. Dose levels for the rats were 0, 15 and 30 mg/kg/day, and for mice were 0, 50 and 100 mg/kg/day. There were no differences in mortality rates or body weights between treated and control mice, and the only non-neoplastic treatment-related effect was an increased incidence of stomach epithelial hyperplasia. In the female rats, there was a significant dose-related ($p=0.007$) increase in thyroid C-cell adenoma/carcinoma; the incidence in the high-dose females was significantly different from control. In male mice, there was a treatment-related increased incidence in hemangiomas/hemangiosarcomas at the high dose and dose-related increased incidences of forestomach carcinoma/papillomas and hepatic carcinomas/papillomas. High-dose female mice displayed an increased incidence of pulmonary adenoma/carcinoma. Most striking was the strong dose-related trend ($p<0.001$) in forestomach carcinomas/papillomas in both male and female mice.

Benzyl chloride was weakly mutagenic in a variety of test systems (Venitt, 1982; Parry and Wilcox, 1982; Arlett, 1982; Topham, 1982). In prokaryotes, it appears to affect point mutations and expresses genotoxicity toward repair-deficient strains. Benzyl chloride induces somatic mutations in Drosophila melanogaster (Fahmy and Fahmy, 1982), but its gene-altering rate in mammalian systems is less well understood.

Leonskaya (1980) found that an oral dose of 208 mg/kg/day on days 1-19 of gestation to rats led to increases in fetal mortality and developmental defects in surviving fetuses. Doses of 0.0006 and 0.006 mg/kg/day were reported to increase fetal mortality and induce a slightly increased incidence of wavy ribs, although the experimental data were not provided. No effects were observed when doses of 0.00006 mg/kg/day were used.

Gavage administration of benzyl chloride in rats at 0.6 mg/kg/day for 6 months led to changes in serum enzymes and whole blood inorganic phosphate levels (Rudnev et al., 1979). Oral doses of 250 and 125 mg/kg benzyl chloride, 3 times/week, were rapidly fatal to rats (Bunner and Creasia, 1982; Lijinsky, 1985). At ≥ 15 mg/kg, rats had hyperplasia or hyperkeratosis of the squamous stomach and hyperplasia or focal necrosis of the heart. Lijinsky (1985) also treated male and female mice by gavage 3 times/week with benzyl chloride for 6-8 months. Doses of 125 and 250 mg/kg were fatal to all rats, whereas the mice exposed to the highest dose (100 mg/kg) survived. In mice, the only treatment-related pathological effect was hepatic hyperplasia. Rats treated with the highest doses had severe chronic gastritis and myocardial damage. Females were more sensitive to the gastric effects of benzyl chloride administration; at both 30 and 62 mg/kg most of these rats had forestomach hyperplasia and/or hyperkeratosis. In a subsequent 2-year bioassay, Lijinsky (1985) observed no non-neoplastic effects in rats at oral doses of up to 30 mg/kg/day benzyl chloride, 3 days/week. Mice not otherwise afflicted with forestomach tumors showed forestomach hyperplasia at 50 or 100 mg/kg/day, 3 days/week.

Based upon the carcinogenic effects of benzyl chloride, it is appropriate to derive a q_1^* to estimate the increased risk of cancer in humans. As seen from Table 5-1, it is appropriate to consider the incidences of forestomach papilloma/carcinoma both in male mice and female mice and the incidences of C-cell adenoma/carcinoma in female rats for q_1^* derivation. Because Lijinsky (1985) did not provide individual animal pathology data, it is not possible to pool the incidences of circulatory system tumors with stomach tumors in the male mice or the lung tumors (marginally significant)

with the stomach tumors in female mice. In any case, it is likely best to treat these tumor types as noninteractive, independent events and tumor progressions.

The data used to calculate the q_1^* values are presented in Table 8-1, 8-2 and 8-3. The transformed doses were calculated by multiplying the experimental dose by 3 days/7 days and by 104 weeks/107.5 weeks. The unadjusted q_1^* values were calculated using the computerized multistage model developed by Howe and Crump (1982). The human q_1^* values were calculated by multiplying the unadjusted value by the cube root of the ratio of the reference human body weight (70 kg) to the animal body weight. Because Lijinsky (1985) did not provide body weight gain data, reference weights of 0.03 kg for mice and 0.35 kg for rats were used as recommended by U.S. EPA (1980b).

As seen from Tables 8-1, 8-2 and 8-3, the data that result in the highest q_1^* of $1.71 \times 10^{-1} \text{ (mg/kg/day)}^{-1}$ are for increased incidences of C-cell adenoma/carcinoma of the thyroid of female rats. This q_1^* is recommended for estimating the increased lifetime risk of cancer for human exposure to benzyl chloride.

TABLE 8-1

Cancer Data Sheet for Derivation of q_1^*

Compound: benzyl chloride
 Reference: Lijinsky, 1985
 Species, Strain, Sex: mice, B6C3F1, male
 Body weight: 0.03 kg (assumed)
 Length of exposure (t_e) = 104 weeks
 Length of experiment (L_e) = 107-108 weeks
 Lifespan of animal (L) = 107-108 weeks
 Tumor site and type: forestomach papilloma and carcinoma
 Route, vehicle: gavage, corn oil

Experimental Doses or Exposures (mg/kg, 3 times/week)	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Examined
100	41.5	32/52
50	20.7	4/52
0	0	0/51

Unadjusted q_1^* from study = 4.2×10^{-3} (mg/kg/day) $^{-1}$

Human q_1^* = 5.57×10^{-2} (mg/kg/day) $^{-1}$

TABLE 8-2

Cancer Data Sheet for Derivation of q_1^*

Compound: benzyl chloride
 Reference: Lijinsky, 1985
 Species, Strain, Sex: mice, B6C3F1, female
 Body weight: 0.03 kg (assumed)
 Length of exposure (t_e) = 104 weeks
 Length of experiment (L_e) = 107-108 weeks
 Lifespan of animal (L) = 104 weeks
 Tumor site and type: forestomach papilloma and carcinoma
 Route, vehicle: gavage, corn oil

Experimental Doses or Exposures (mg/kg, 3 times/week)	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Examined
100	41.5	19/51
50	20.7	5/50
0	0	0/52

Unadjusted q_1^* from study = 9.2×10^{-3} (mg/kg/day) $^{-1}$

Human q_1^* = 1.2×10^{-1} (mg/kg/day) $^{-1}$

TABLE 8-3

Cancer Data Sheet for Derivation of q_1^*

Compound: benzyl chloride

Reference: Lijinsky, 1985

Species, Strain, Sex: rat, Fischer 344, female

Body weight: 0.35 kg (assumed)

Length of exposure (t_e) = 104 weeksLength of experiment (t_e) = 107-108 weeksLifespan of animal (L) = 107-108 weeks

Tumor site and type: thyroid, C-cell adenoma/carcinoma

Route, vehicle: gavage, corn oil

Experimental Doses or Exposures (mg/kg, 3 times/week)	Transformed Dose (mg/kg/day)	Incidence No. Responding/No. Examined
30	12.4	14/52
15	6.2	8/51
0	0	4/52

Unadjusted q_1^* from study = 2.9×10^{-2} (mg/kg/day) $^{-1}$ Human q_1^* = 1.7×10^{-1} (mg/kg/day) $^{-1}$

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

The chronic and subchronic toxicity studies and a teratology study of benzyl chloride were discussed in Chapter 5 and are summarized in Table 9-1.

Since Rudnev et al. (1979) and Leonskaya (1980) provided no experimental data, thereby limiting the reliability of the reported dose-response data, these studies are not appropriate for RQ determination.

As seen from Table 9-1, effects of subchronic oral exposure to benzyl chloride in rats are death at transformed doses ≥ 25.6 mg/kg/day and hyperplasia/hyperkeratosis of the stomach and hyperplasia/focal necrosis of the heart at transformed doses ≥ 6.4 mg/kg/day (Bunner and Creasia, 1982; Lijinsky, 1985). Because the deaths of the rats appeared to represent acute responses to relatively high doses, this effect cannot be considered for RQ derivation. Moderate to severe hepatic hyperplasia occurred in mice treated with ≥ 2.7 mg/kg/day for 26 weeks (Lijinsky, 1985). In the 2-year carcinogenicity study, mice treated with ≥ 21.4 mg/kg/day had increased incidences of squamous cell tumors in the stomach; the only non-neoplastic effect was epithelial hyperplasia of the stomach in mice that did not have stomach tumors. Because equally or more severe effects were observed at lower doses in the subchronic studies than in the 2-year study, it is more appropriate to base the RQ on the subchronic studies; no uncertainty factor of 10 is needed.

The most severe effect in rats is myocardial necrosis, which Bunner and Creasia (1982) implied occurred at a dose as low as 6.4 mg/kg/day. Multiplying the dose by the cube root of ratio of the body weight of the rat (0.35 kg) to the reference human body weight (70 kg), and by 70 kg results

TABLE 9-1

Oral Toxicity Summary for Subchronic and Chronic Administration of Benzyl Chloride by Gavage in Laboratory Animals

Species/ Strain	Sex	Number at Start	Average Weight (kg) (assumed)	Vehicle/ Physical State	Purity	Exposure	Transformed Animal Dose (mg/kg/day)	Response	Reference
Rat/NR	NR	15/dose group	0.35	corn oil	NR	0, 0.6, 0.06 or 0.006 mg/kg/day	0, 0.6, 0.06 or 0.006	Elevation in blood inorganic phosphate and changes in the activities of serum enzymes at high dose.	Rudnev et al., 1979
Rat/NR	F	20/group	0.35	sunflower oil	NR	0, 0.00006, 0.0006, 0.006 or 208 mg/kg/day during days 1-19 of gestation	0, 0.00006, 0.0006, 0.006 or 208	Increased fetal mortality. Increased incidence of wavy ribs, decreased crown-rump length at ≥ 0.0006 mg/kg/day	Leonskaya, 1980
Rat/SPF - Fischer 344/N	M	10/dose group	0.35	corn oil	97.5-98%	0, 15, 30, 62, 125 or 250 mg/kg/day, 3 times/week for 37 weeks	0, 6.4, 12.8, 25.6, 51.2 or 102.4	Two highest doses fatal to all rats. At ≥ 6.4 mg/kg/day, hyperplasia, hyperkeratosis of stomach, hyperplasia and necrosis of heart	Bunner and Creasia, 1982; Lijinsky, 1985
Rat/NR SPF -Fischer 344/N	F	10/dose group	NR	corn oil	97.5-98%	0, 15, 30, 62, 125 or 250 mg/kg/day, 3 times/week for 27 weeks	0, 6.4, 12.8, 25.6, 51.2 or 102.4	Two highest doses fatal to all rats. ≥ 6.4 mg/kg/day killed 6/10; squamous stomach hyperkeratosis or hyperplasia and hyperplasia or necrosis of heart at 6.4 mg/kg/day	Bunner and Creasia, 1982 Lijinsky, 1985
Mouse/ B6C3F1	M F	10/dose group	0.03	corn oil	97.5-98%	0, 6.3, 12.5, 25, 50 or 100 mg/kg/day, 3 times/week for 26 weeks	0, 2.7, 5.4, 10.7, 21.4 or 42.9	Moderate to severe hepatic hyperplasia	Lijinsky, 1985
Rat/SPF - Fischer 344/N	M F	52/sex/ dose group	0.35	corn oil	97.5-98%	0, 15 or 30 mg/kg/day, 3 times/week for 104 weeks, sacrificed at 108 weeks	0, 6.4 or 12.9	No treatment-related non- neoplastic effects	Lijinsky, 1985
Mouse/ B6C3F1	M F	52/sex/ dose group	0.03	corn oil	97.5-98%	0, 50 or 100 mg/kg/ day, 3 times/week for 104 weeks, sacrificed at 108 weeks	0, 21.4 or 42.9	Treatment-related stomach epithelial hyperplasia in mice without stomach tumors	Lijinsky, 1985

*Transformed animal doses were calculated by multiplying the dose by 3 days/7 days, when necessary.

NR = Not reported

in an MED of 76.6 mg/day, which corresponds to an RV_d of 2.7. An RV_e of 6 is assigned to necrosis. Multiplying the RV_d by the RV_e results in a CS of 16.2, which corresponds to an RQ of 1000 (Table 9-2).

In mice, there was liver hyperplasia at ≥ 2.7 mg/kg/day. Multiplying the dose by the cube root of the ratio of the mouse body weight (0.03 kg) to the human weight, and by 70 kg results in an MED of 14.2 mg/day, which corresponds to an RV_d of 3.8. The RV_e for hyperplasia is 4 and the CS is 15.2, which also corresponds to an RQ of 1000 (see Table 9-2).

Since the higher CS is derived from the data for rats, these data are recommended as the basis for the RQ (Table 9-3).

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

Parenteral and topical administration of benzyl chloride to laboratory animals has been shown to induce local, and occasionally metastatic, tumors (Druckrey et al., 1970; Coombs, 1982a,b). In none of these studies, however, was benzyl chloride considered more than a weak carcinogen. Other authors (Poirier et al., 1975; Fukuda et al., 1981; Ashby et al., 1982) have found no significant differences in tumor incidence between control and treated animals. The studies by Coombs (1982a,b) and Ashby et al. (1982) suggest that, when applied topically, benzyl chloride acts as a tumor initiator; however, since there are so many strain, dose, and methodology differences between these studies generalizations about the carcinogenic potential of benzyl chloride are difficult. Moreover, in none of the studies was a treatment period of 2 years allowed for assessment of late tumorigenesis. Despite limitations in methodology in these early animal studies, IARC (1982) considered benzyl chloride a weak carcinogen.

TABLE 9-2
Composite Scores for the Oral Toxicity of Benzyl Chloride

Species	Animal Dose (mg/kg/day)	Chronic Human MED (mg/day)	RVd	Effect	RVe	CS	RQ	Reference
Rat	6.4	76.6	2.7	myocardial necrosis	6	16.2	1000	Lijinsky, 1985; Bunner and Creasia, 1982
Mouse	2.7	14.2	3.8	moderate to severe hyperplasia in liver	4	15.2	1000	Lijinsky, 1985

TABLE 9-3

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	oral
Dose*:	76.6 mg/day
Effect:	myocardial necrosis
Reference:	Lijinsky, 1985; Bunner and Creasia, 1982
RV _d :	2.7
RV _e :	6
Composite Score:	16.2
RQ:	1000

*Equivalent human dose

As seen in Tables 5-2, 5-3 and 5-4 workers exposed occupationally to the intermediates in benzoyl chloride production showed increases in respiratory and digestive system cancers (Sorahan et al., 1983; Wong and Morgan, 1984; Sakabe et al., 1976; Sakabe and Fukuda, 1977). Because of small sample sizes, lack of data on cigarette smoking and the fact that exposure was to a mixture of halogenated intermediates, these data are of little value in determining the threat to human health of benzyl chloride exposure.

The ability of benzyl chloride to induce neoplasia was addressed in the 2-year chronic bioassay by Lijinsky (1985) (see Table 5-1). In this study, there were positive dose-related trends in the incidences of forestomach papillomas/carcinomas in mice given 0, 50 and 100 mg/kg benzyl chloride, 3 times/week. Similarly, there were treatment-related increases in hemangiomas/hemangiosarcomas and hepatic tumors in male mice, and treatment-related increases in respiratory tract tumors in females. In rats given 0, 15 or 30 mg/kg benzyl chloride, 3 times/week, there were significantly increased incidences of thyroid C-cell tumors in females. In light of the multiple-site tumor incidence in the Lijinsky (1985) study and the equivocal neoplastic responses in exposed workers, benzyl chloride should be classified as a IARC Group 2B chemical or B2, probable carcinogen, using the U.S. EPA, CAG system.

In the preliminary assessment of the carcinogenic potency of benzyl chloride, U.S. EPA (1983b) stated that there was insufficient evidence for determination of a potency factor. Given the data available at that time, the U.S. EPA (1983b) considered benzyl chloride to be an IARC Class 3 carcinogen.

The F-factor for benzyl chloride can be calculated from the incidence of forestomach tumors in either male or female mice and for C-cell tumors in female rats (Lijinsky, 1985). The highest F-value was calculated for the data in male mice (Table 9-4). The unadjusted $1/ED_{10}$ was obtained using the computerized multistage model developed by Howe and Crump (1982). It was multiplied by the cube root of the ratio of human body weight (assumed to be 70 kg) to the mouse body weight (assumed to be 0.03 kg), to obtain an F-factor of $8.68 \times 10^{-1} \text{ (mg/kg/day)}^{-1}$ (see Table 9-4). Because the F-factor is <1 and benzyl chloride belongs to IARC group 2B, it has a LOW hazard ranking under CERCLA.

TABLE 9 4

Derivation of Potency Factor (F) for Benzyl Chloride

Reference:	Lijinsky, 1985
Exposure route:	oral
Species:	mouse
Strain:	B6C3F1
Sex:	male
Vehicle or physical state:	corn oil
Body weight:	0.030 kg (assumed)
Duration of treatment:	104 weeks
Duration of study:	107-108 weeks
Lifespan of human:	104 weeks
Target organ:	forestomach
Tumor type:	papilloma/carcinoma
Experimental doses/exposure:	0, 50, 100 mg/kg/day, 3 days/week
Transformed dose (mg/kg/day):	0, 20.7, 41.7
Tumor incidence:	0/51, 4/52, 32/52
Unadjusted 1/ED ₁₀ :	$6.5407357 \times 10^{-2} \text{ (mg/kg/day)}^{-1}$
Adjusted 1/ED ₁₀ (F factor):	8.6753205×10^{-1}

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APPENDIX
LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN Internation
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
FEDERAL REGISTER

These searches were conducted in October, 1985. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation through 1984). Cincinnati, OH. 486 p.

ACGIH (American Conference of Governmental Industrial Hygienists). 1985. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1985-1986. Cincinnati, OH. 114 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. p. 2878.

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ITII (International Technology Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

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USITC (U.S. International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982, USITC Publ. 1422. Washington, DC.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd ed. Van Nostrand Reinhold Co., NY.

Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

Windholz, M., Ed. 1983. The Merck Index, 10th ed. Merck and Co., Inc., Rahway, NJ.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. United States Dept. Interior, Fish and Wildlife Service. Resource Publ. 137. Washington, DC.

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Pimental, D. 1971. Ecological Effect of Pesticides on Non-Target Species. PB-269605. Prepared for the U.S. EPA, Washington, DC.

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